Harris, A.
09/989388

-key terms

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      FILE 'REGISTRY' ENTERED AT 14:45:27 ON 26 JUN 2003
                   E "LYS-PLASMINOGEN"/CN 5
L1                3 S "LYS-PLASMINOGEN"?/CN
                   E PLASMINOGEN/CN 5
L2              674 S PLASMINOGEN ?/CN
                   E HEPARIN/CN 5
L3                1 S E3

                   E PLASMIN/CN 5
L5               41 S PLASMIN ?/CN
                   E TRANEXAMIC ACID/CN 5
L6                1 S E3

      FILE 'HCAPLUS' ENTERED AT 15:11:55 ON 26 JUN 2003
L1                3 SEA FILE=REGISTRY ABB=ON  PLU=ON  "LYS-PLASMINOGEN"?/CN
L2              674 SEA FILE=REGISTRY ABB=ON  PLU=ON  PLASMINOGEN ?/CN
L3                1 SEA FILE=REGISTRY ABB=ON  PLU=ON  HEPARIN/CN
L4             1307 SEA FILE=HCAPLUS ABB=ON  PLU=ON  (L1 OR L2 OR PLASMINOGEN
                    ) AND (L3 OR HEPARIN)
L5               41 SEA FILE=REGISTRY ABB=ON  PLU=ON  PLASMIN ?/CN
L6                1 SEA FILE=REGISTRY ABB=ON  PLU=ON  "TRANEXAMIC ACID"/CN
L7              301 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L4 AND (L5 OR L6 OR
                    PLASMIN OR TRANEXAMIC)
L8               29 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L7 AND (TUMOUR OR TUMOR
                    OR NEOPLAS? OR CANCER? OR CARCIN? OR ANTICANCER? OR
                    ANTICARCIN? OR ANTINEOPLAS? OR ANTITUMOUR OR ANTITUMOR)

L8   ANSWER 1 OF 29  HCAPLUS  COPYRIGHT 2003 ACS
ACCESSION NUMBER:        2003:428737  HCAPLUS
TITLE:                   Small molecule inhibitors of urokinase-type
                         plasminogen activator
AUTHOR(S):               Rockway, Todd W.
CORPORATE SOURCE:        AP52N, R47D, Abbott Laboratories, Global
                         Pharmaceutical Research and Development, 200
                         Abbott Park Road, Abbott Park, IL, 60064-6217,
                         USA
SOURCE:                  Expert Opinion on Therapeutic Patents (2003),
                         13(6), 773-786
                         CODEN: EOTPEG; ISSN: 1354-3776
PUBLISHER:               Ashley Publications Ltd.
DOCUMENT TYPE:           Journal
LANGUAGE:                English
AB   The urokinase-type plasminogen activator (uPA) protein is
     a multifunctional protein involved in a myriad of biol. activities
     including extracellular matrix degrdn. and cell invasion.  Active
     uPA is a 411 amino acid protein consisting of 3 domains, each of
     which confers a particular biol. function to the overall protein.
     The amino terminal domain or growth factor domain (GFD), comprised
     of amino acid residues 1 - 48, is involved in uPA interaction with
     its cell surface receptor, urokinase-type plasminogen
     activator receptor (UPAR).  The interaction of uPA with UPAR
     promotes, in part, cell adhesion, migration and invasion.  A second
     domain is the kringle domain, comprising amino acid residues 49 -
     135.  Initially thought to bind heparin, the kringle
     domain has more recently been shown to possess antiangiogenic
     activity.  A third domain comprising amino acid residues 159 - 411,
     the serine protease domain, is involved in the proteolytic
     activation of plasminogen to plasmin.  The
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prodn. of **plasmin** by uPA begins a cascade of events manifested by extracellular matrix degrdn. The recent patent literature describes small mol. compds., which inhibit the interaction of uPA with UPAR, inhibit the proteolytic activity of the uPA serine protease domain and inhibit the interaction of uPA with its natural inhibitor, **plasminogen** activator inhibitor-1 (PAI-1). Small peptides encompassing residues 19 - 31 of the GFD have been developed which exhibit potent inhibition of the uPA-UPAR interaction and show efficacy in **tumor** -bearing animal models. Small mols. have been disclosed by Corvas, which are reported to be inhibitors of PAI-1. Finally, two approaches toward the development of inhibitors of the uPA serine protease domain have been described in the recent patent literature. The first approach describes non-covalent peptidederived inhibitors discovered by phage display techniques, which bind in the substrate-binding groove of the uPA active site. An alternative approach describes non-covalent small mol. inhibitors, which bind in the enzyme active site in a slightly different binding mode than the peptide-derived inhibitors. These small mol. non-peptide analogs inhibit the uPA proteolytic activity quite effectively and are reported to possess excellent enzyme selectivity and highly improved oral activity. The clin. utility of small mol. uPA enzyme inhibitor analogs awaits the results of a preliminary clin. evaluation of compds. described by Wilex.

L8 ANSWER 2 OF 29 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2003:390758 HCAPLUS
DOCUMENT NUMBER: 138:390934
TITLE: Topical and transdermal administration of peptidyl drugs with hydroxide-releasing agents as skin permeation enhancers
INVENTOR(S): Luo, Eric C.; Jacobson, Eric C.; Hsu, Tsung-Min
PATENT ASSIGNEE(S): Dermatrends, Inc., USA
SOURCE: U.S., 13 pp., Cont.-in-part of U.S. Ser. No. 569,889.
CODEN: USXXAM
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 22
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 6565879	B1	20030520	US 2000-687937	20001013
US 2001038862	A1	20011108	US 2000-737831	20001214
US 6558695	B2	20030506		

PRIORITY APPLN. INFO.: US 1999-465098 A2 19991216
US 2000-569889 A2 20000511
US 2000-687937 A2 20001013

AB A method is provided for increasing the permeability of skin or mucosal tissue to a topically or transdermally administered pharmacol. or cosmeceutically active peptide, polypeptide or protein. The method involves use of a specified amt. of a hydroxide-releasing agent, the amt. optimized to increase the flux of the peptide, polypeptide or protein through a body surface while minimizing the likelihood of skin damage, irritation or sensitization. Formulations and drug delivery devices employing hydroxide-releasing agents as permeation enhancers are provided as

well. An in vitro human cadaver skin permeation study was conducted using 0.18% leuprolide soln. and 3.6% sodium hydroxide.

IT **9001-91-6, Plasminogen 105857-23-6,** Alteplase **139639-23-9,** Tissue **plasminogen** activator
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(topical and transdermal administration of peptidyl drugs with hydroxide-releasing agents as skin permeation enhancers)

REFERENCE COUNT: 39 THERE ARE 39 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L8 ANSWER 3 OF 29 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2002:933518 HCAPLUS
DOCUMENT NUMBER: 138:248633
TITLE: A truncated **plasminogen** activator inhibitor-1 protein blocks the availability of **heparin**-binding vascular endothelial growth factor A isoforms
AUTHOR(S): Mulligan-Kehoe, Mary Jo; Kleinman, Hynda K.; Drinane, Mary; Wagner, Robert J.; Wieland, Courtney; Powell, Richard J.
CORPORATE SOURCE: Dep. Surg., Vascular Surg. Sect., Dartmouth Med. Sch., Dartmouth Coll., Hanover, NH, 03756, USA
SOURCE: Journal of Biological Chemistry (2002), 277(50), 49077-49089
CODEN: JBCHA3; ISSN: 0021-9258
PUBLISHER: American Society for Biochemistry and Molecular Biology
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The authors have made deletions of the porcine **plasminogen** activator inhibitor-1 (PAI-1) gene to obtain recombinant truncated PAI-1 proteins to examine functions of the PAI-1 isoforms. The authors previously reported that one recombinant truncated protein, rPAI-123, induces the formation of angiostatin by cleaving **plasmin**. The rPAI-123 protein is also able to bind urokinase **plasminogen** activator and **plasminogen** and then reduce the amt. of **plasmin** that is formed. The authors have now prepd. three different truncated rPAI-1 proteins and demonstrate that PAI-1 conformations control the release of **heparin**-binding vascular endothelial growth factor (VEGF) isoforms. The rPAI-123 isoform can regulate the functional activity of heparan sulfate-binding VEGF-A isoforms by blocking the activation of VEGF from heparan sulfate. The rPAI-123 conformation induced extensive apoptosis in cultured endothelial cells and thus reduced the no. of proliferating cells. The rPAI-123 isoform inhibited migration of VEGF-stimulated sprouting from chick aortic rings by 65%, thus displaying a role in anti-angiogenic mechanisms. This insight into anti-angiogenic functions related to PAI-1 conformational changes could provide potential intervention points in angiogenesis assocd. with atherosclerotic plaques and **cancer.**

IT **140208-23-7, Plasminogen** activator inhibitor-1
RL: BSU (Biological study, unclassified); PRP (Properties); BIOL (Biological study)
(recombinant(r)PAI-123, rPAI-124, rPIA-1HEP23 and rPIA-1.DELTA.23; truncated **plasminogen** activator

inhibitor-1 protein blocks availability of **heparin**
-binding vascular endothelial growth factor A isoforms)

IT **9001-91-6, Plasminogen 9005-49-6,**
Heparin, biological studies
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(truncated **plasminogen** activator inhibitor-1 protein
blocks availability of **heparin**-binding vascular
endothelial growth factor A isoforms)

REFERENCE COUNT: 77 THERE ARE 77 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L8 ANSWER 4 OF 29 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2002:907166 HCAPLUS
DOCUMENT NUMBER: 138:322
TITLE: Plasma glucosylceramide deficiency as risk factor for thrombosis and modulator of anticoagulant protein C
INVENTOR(S): Griffin, John H.; Deguchi, Hiroshi; Fernandez, Jose
PATENT ASSIGNEE(S): USA
SOURCE: U.S. Pat. Appl. Publ., 32 pp.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 2002177563	A1	20021128	US 2002-86943	20020228
WO 2002102325	A2	20021227	WO 2002-US6340	20020228

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.: US 2001-272103P P 20010228
US 2001-278045P P 20010322

AB The present invention has detd. that exogenously added glucosylceramide (GlcCer) and other neutral glycolipids such as the homologous Glc-contg. globotriaosylceramide (Gb3Cer), dose-dependently prolonged clotting times of normal plasma in the presence but not absence of APC:protein S, indicating GlcCer or Gb3Cer can enhance protein C pathway anticoagulant activity. In studies using purified proteins, inactivation of factor Va by APC:protein S was enhanced by GlcCer alone and by GlcCer, globotriaosylceramide, lactosylceramide, and galactosylceramide in multicomponent vesicles contg. phosphatidylserine and phosphatidylcholine. Thus, the present invention provides neutral glycolipids such as GlcCer and Gb3Cer, as anticoagulant cofactors that contribute to the antithrombotic activity of the protein C

pathway. The present invention has also detd. that a deficiency of plasma GlcCer is a risk factor for thrombosis. Methods are provided to det. individuals at risk for thrombosis, methods of treatment as well as methods of screening for antithrombotic factors from neutral glycolipids.

IT **9001-91-6D, Plasminogen**, acylated and acylated complexes with streptokinase **9005-49-6, Heparin**, biological studies **9005-49-6D, Heparin**, analogs **139639-23-9**, Tissue **plasminogen** activator **139639-23-9D**, Tissue **plasminogen** activator, analogs
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(plasma glucosylceramide or other neutral glycolipid deficiency as risk factor for thrombosis and modulator of anticoagulant protein C when given in vesicle form in relation to combination with other agents)

L8 ANSWER 5 OF 29 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2002:716853 HCAPLUS
DOCUMENT NUMBER: 137:253055
TITLE: Biopolymer membrane and methods for its preparation
INVENTOR(S): Delmotte, Yves
PATENT ASSIGNEE(S): Belg.
SOURCE: U.S. Pat. Appl. Publ., 23 pp., Cont.-in-part of U.S. Ser. No. 566,372.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 4
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 2002131933	A1	20020919	US 2001-4257	20011026
WO 9622115	A1	19960725	WO 1996-EP160	19960116
W: AU, CA, JP, US				
RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
US 6461325	B1	20021008	US 1999-386198	19990831
WO 2003035115	A2	20030501	WO 2002-US34408	20021028
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VC, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				

PRIORITY APPLN. INFO.:

WO 1996-EP160	A2	19960116
US 1996-679658	A2	19960712
US 1999-386198	A2	19990831
US 2000-566372	A2	20000509
DE 1995-19501067	A	19950116

US 2001-4257 A 20011026

AB A biopolymer membrane in its substantially dry form having a thickness less than about 75 .mu., a solvent content less than about 5% by wt. of the membrane, a radius of curvature of less than about 5 cm, a d. greater than about 1 g/cm3, and a max. pore size of about 20 .mu.m is claimed. Twenty milliliters at 80 mg/mL of Tissucol (a multicomponent tissue adhesive) was dissolved in an aq. aprotinin soln. having 3000 KIU/mL and then dild. at a 1:4 ratio with distd. water to yield a fibrinogen concn. of approx. 20 mg/mL. Approx. 20 mL of this soln. was rapidly mixed with 20 mL of a thrombin-CaCl2 soln. (human thrombin, approx. 10 IU/mL and 5 mM CaCl2) and poured into a Petri dish, and then incubated for approx. 16 h in a humid chamber at 37.degree.. The clot in the form of a round disk having a thickness of approx. 7 mm was then deep-frozen and lyophilized. The flat material was incubated for approx. 3 h in humid chamber at room temp., whereby a soft, adaptable and highly absorbent biopolymer product was obtained. The biopolymer product had a residual moisture content of about 15% and a water absorption capacity of approx. 3-fold of its own wt. The biopolymer product was then wetted with water for about 15 min to substantially fill it with water, then compressed between two pieces of microporous polyethylene terephthalate film to define a biopolymer membrane. The microporous film had a thickness of about 5 mm and a porosity of about 5.0 mm. The thickness of the biopolymer product was about 7 mm before compression and about 75 .mu.m thereafter and had less than about 2% water by wt. and a sp. gr. or d. of about 1.77 g/cm3.

IT **1197-18-8, Tranexamic** acid **9001-91-6, Plasminogen,**
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(biopolymer membrane and methods for its prepn.)

IT **9005-49-6, Heparin,** biological studies
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(growth factor for bond of; biopolymer membrane and methods for its prepn.)

IT **139639-23-9,** Tissue **plasminogen** activator
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(photoactivable; biopolymer membrane and methods for its prepn.)

L8 ANSWER 6 OF 29 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2001:817206 HCAPLUS
DOCUMENT NUMBER: 135:362582
TITLE: Topical and transdermal administration of peptide drugs using hydroxide releasing agents as permeation enhancers
INVENTOR(S): Luo, Eric C.; Hsu, Tsung-Min
PATENT ASSIGNEE(S): Dermatrends, Inc., USA
SOURCE: U.S. Pat. Appl. Publ., 16 pp., Cont.-in-part of U.S. Ser. No. 687,937.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 22
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 2001038862	A1	20011108	US 2000-737831	20001214
US 6558695	B2	20030506		

US 6565879 B1 20030520 US 2000-687937 20001013
PRIORITY APPLN. INFO.: US 1999-465098 A2 19991216
US 2000-569889 A2 20000511
US 2000-687937 A2 20001013

AB A method is provided for increasing the permeability of skin or mucosal tissue to a topically or transdermally administered pharmacol. or cosmeceutically active peptide, polypeptide or protein. The method involves use of a specified amt. of a hydroxide-releasing agent, the amt. optimized to increase the flux of the peptide, polypeptide or protein through a body surface while minimizing the likelihood of skin damage, irritation or sensitization. Formulations and drug delivery devices employing hydroxide-releasing agents as permeation enhancers are provided as well. The in-vitro permeation of oxytocin through human cadaver skin was performed by using Franz-type diffusion cells with a diffusion area of 1 cm2. The cumulative amt. of oxytocin across human cadaver skin was calcd. by using the measured oxytocin concns. in the receiver solns. for each time point.

IT **9001-91-6, Plasminogen 105857-23-6,** Alteplase **139639-23-9,** Tissue **plasminogen** activator
RL: BPR (Biological process); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)
(topical and transdermal administration of peptide drugs using hydroxide releasing agents as permeation enhancers)

L8 ANSWER 7 OF 29 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2001:798040 HCAPLUS
DOCUMENT NUMBER: 135:339222
TITLE: Inhibition of abnormal cell proliferation with camptothecin or a derivative, analog, metabolite, or prodrug thereof, and combinations including camptothecin
INVENTOR(S): Rubinfeld, Joseph
PATENT ASSIGNEE(S): Supergen, Inc., USA
SOURCE: PCT Int. Appl., 38 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 3
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001080843	A2	20011101	WO 2001-US12848	20010419
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
US 6420378	B1	20020716	US 2000-553710	20000420

EP 1276479 A2 20030122 EP 2001-930607 20010419
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR
PRIORITY APPLN. INFO.: US 2000-553710 A1 20000420
US 1999-418862 A2 19991015
WO 2001-US12848 W 20010419

AB A method for treating diseases assocd. with abnormal cell proliferation comprises delivering to a patient in need of treatment a compd. selected from 20(S)-comptothecin, an analog of 20(S)-comptothecin, a deriv. of 20(S)-camptothecin, a prodrug of 20(S)-camptothecin, and pharmaceutically active metabolite of 20(S)-camptothecin, in combination with an effective amt. of one or more agents selected form the group consisting of alkylating agent, antibiotic agent, antimetabolic agent, hormonal agent, plant-derived agent, anti-angiogenesis agent and biol. agent. The method can be used to treat benign **tumors**, malignant or metastatic **tumors**, leukemia and diseases assocd. with abnormal angiogenesis.

IT **9005-49-6, Heparin**, biological studies
138757-15-0, .alpha.2-Antiplasmin **140208-23-7**, PAI-1 **142243-03-6**, Proteinase inhibitor PAI-2
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(camptothecin or deriv., analog, metabolite, or prodrug thereof for inhibition of abnormal cell proliferation, and combinations including camptothecin)

L8 ANSWER 8 OF 29 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2001:636107 HCAPLUS
DOCUMENT NUMBER: 135:190417
TITLE: Inhibiting angiogenesis using molecules that enhance **plasmin** formation or prolong **plasmin** activity
INVENTOR(S): Gebbink, Martijn Frans Ben Gerard; Voest, Emile Eugene
PATENT ASSIGNEE(S): Universitair Medisch Centrum Utrecht, Neth.; Universiteit Utrecht
SOURCE: PCT Int. Appl., 29 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001062799	A2	20010830	WO 2001-NL155	20010226
WO 2001062799	A3	20020404		

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE,

TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

EP 1130031 A1 20010905 EP 2000-200664 20000225
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO

EP 1257582 A2 20021120 EP 2001-912573 20010226
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR

US 2003050245 A1 20030313 US 2002-229394 20020826

PRIORITY APPLN. INFO.: EP 2000-200664 A 20000225
WO 2001-NL155 W 20010226

AB The invention provides a proteinaceous mol. comprising a lysine and/or arginine residue and/or a functional equiv. thereof, capable of providing enhanced levels of **plasmin** in a mammalian through tPA mediated **plasminogen** activation for use as a pharmaceutical. The invention further provides use of a proteinaceous mol. according to the invention for the prepn. of a medicament for the treatment of diseases related with angiogenesis and/or inflammatory disorders and/or conformational disorders and/or ageing. Furthermore the invention provides a proteinaceous mol. to suppress **tumor** growth, to regress established **tumors**, to degrade amyloid-.beta. and to inhibit amyloid-.beta. action. Addnl. the invention provides a method for the treatment of a disease assocd. with or dependent on angiogenesis and/or assocd. with amyloid deposition comprising administering to a patient an effective amt. of a proteinaceous mol. comprising a lysine and/or arginine residue and/or a functional equiv. thereof, capable of providing enhanced levels of **plasmin** in a mammalian through tPA mediated **plasminogen** activation.

IT **9001-91-6, Plasminogen**
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(activation; inhibiting angiogenesis using mols. that enhance **plasmin** formation or prolong **plasmin** activity)

IT **139639-23-9**, Tissue-type **plasminogen** activator
RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)
(inhibiting angiogenesis using mols. that enhance **plasmin** formation or prolong **plasmin** activity)

IT **9005-49-6, Heparin**, biological studies
RL: BPR (Biological process); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)
(inhibiting angiogenesis using mols. that enhance **plasmin** formation or prolong **plasmin** activity)

L8 ANSWER 9 OF 29 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2001:402997 HCAPLUS
DOCUMENT NUMBER: 135:329815
TITLE: Differential regulation of cell proliferation and protease secretion by epidermal growth factor and amphiregulin in tumoral versus normal breast epithelial cells
AUTHOR(S): Silvy, M.; Giusti, C.; Martin, P.-M.; Berthois, Y.
CORPORATE SOURCE: Laboratoire de Cancerologie Experimentale,

Marseille, 13916, Fr.
SOURCE: British Journal of Cancer (2001), 84(7), 936-945
CODEN: BJCAAI; ISSN: 0007-0920
PUBLISHER: Harcourt Publishers Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Amphiregulin (AR) is a **heparin**-binding epidermal growth factor (EGF)-related peptide that seems to play an important role in mammary epithelial cell growth regulation. We have investigated the regulation of AR-gene expression and -protein secretion by EGF in normal breast epithelial cells (HMECs), as well as in the tumoral breast epithelial cell lines MCF-7 and MDA-MB231. EGF induced a dose-dependent increase of AR mRNA level in both normal and tumoral cells. Thus, 10-8 M EGF stimulated AR expression in HMECs to 140-300% of control. A similar EGF concn. increased AR mRNA level to 550% and 980% of control in MCF-7 and MDA-MB231 cells, resp. This was accompanied by an accumulation of AR into conditioned culture media. However, HMECs secreted in response to EGF, 5-10 fold more AR than **tumor** cells. Furthermore, the potential participation of AR in the regulation of the **plasminogen** activator (PA)/**plasmin** system was investigated. Whereas HMEC-proliferation was stimulated by AR, the levels of secreted urokinase-type **plasminogen** activator (uPA) and type-1 **plasminogen** activator inhibitor (PAI-1) remained unaffected. Conversely, AR failed to regulate the proliferation of tumoral cell lines but induced an accumulation of uPA and PAI-1 into culture media. This was accompanied by an increase of the no. of tumoral cells that invaded matrigel in vitro. Moreover, the presence of a neutralizing anti-uPA receptor antibody reversed the increased invasiveness of MDA-MB231 cells induced by AR. These data reveal differential behavior of normal vs. tumoral breast epithelial cells in regard to the action of AR and demonstrate that, in a no. of cases, AR might play a significant role in **tumor** progression through the regulation of the PA/**plasmin** system.

IT **140208-23-7**, Type 1 **plasminogen** activator inhibitor
RL: BOC (Biological occurrence); BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); OCCU (Occurrence); PROC (Process)
(differential regulation of cell proliferation and protease secretion by EGF and amphiregulin in tumoral vs. normal breast epithelial cells)

REFERENCE COUNT: 33 THERE ARE 33 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L8 ANSWER 10 OF 29 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2000:240983 HCAPLUS
DOCUMENT NUMBER: 132:260687
TITLE: Antithrombin III compositions and methods for inhibiting angiogenesis
INVENTOR(S): O'Reilly, Michael S.; Pirie-Shepherd, Steven; Folkman, M. Judah
PATENT ASSIGNEE(S): Children's Hospital, USA
SOURCE: PCT Int. Appl., 66 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent

LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000020026	A2	20000413	WO 1999-US23450	19991008
WO 2000020026	A3	20000908		
W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
CA 2344613	AA	20000413	CA 1999-2344613	19991008
EP 1117428	A2	20010725	EP 1999-954789	19991008
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
US 2002076413	A1	20020620	US 1999-414834	19991008
JP 2002526418	T2	20020820	JP 2000-573385	19991008

PRIORITY APPLN. INFO.:
US 1998-103526P P 19981008
US 1999-116131P P 19990115
WO 1999-US23450 W 19991008

AB Methods are provided for reducing or inhibiting angiogenesis, **tumor** growth and endothelial cell proliferation by the administration of compns. contg. fragments, conformations, biol. equiv., or derivs. of antithrombin III. The invention also provides pharmaceutical compns. comprising a fragment, conformation, biol. equiv., or deriv. of antithrombin III, as well as methods of identifying novel inhibitors of **tumor** growth, endothelial cell proliferation, and/or angiogenesis. The invention also relates to compns. and methods for altering angiogenesis in a mammal, as well as to methods of treatment for disorders assocd. with angiogenesis (e.g., **cancer**).

IT **138757-15-0D**, .alpha.2-Antiplasmin, conformational variants **140208-23-7D**, **Plasminogen** activator inhibitor 1, conformational variants **148196-69-4D**, Protease nexin 1, conformational variants
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(Antithrombin III compns. and methods for inhibiting angiogenesis)

L8 ANSWER 11 OF 29 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1999:795994 HCAPLUS
DOCUMENT NUMBER: 132:31744
TITLE: Gene probes used for genetic profiling in healthcare screening and planning
INVENTOR(S): Roberts, Gareth Wyn
PATENT ASSIGNEE(S): Genostic Pharma Ltd., UK
SOURCE: PCT Int. Appl., 745 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English

FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9964627	A2	19991216	WO 1999-GB1780	19990604

W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM

RW: GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.:

GB 1998-12099	A	19980606
GB 1998-13291	A	19980620
GB 1998-13611	A	19980624
GB 1998-13835	A	19980627
GB 1998-14110	A	19980701
GB 1998-14580	A	19980707
GB 1998-15438	A	19980716
GB 1998-15574	A	19980718
GB 1998-15576	A	19980718
GB 1998-16085	A	19980724
GB 1998-16086	A	19980724
GB 1998-16921	A	19980805
GB 1998-17097	A	19980807
GB 1998-17200	A	19980808
GB 1998-17632	A	19980814
GB 1998-17943	A	19980819

AB There is considerable evidence that significant factor underlying the individual variability in response to disease, therapy and prognosis lies in a person's genetic make-up. There have been numerous examples relating that polymorphisms within a given gene can alter the functionality of the protein encoded by that gene thus leading to a variable physiol. response. In order to bring about the integration of genomics into medical practice and enable design and building of a technol. platform which will enable the everyday practice of mol. medicine a way must be invented for the DNA sequence data to be aligned with the identification of genes central to the induction, development, progression and outcome of disease or physiol. states of interest. According to the invention, the no. of genes and their configurations (mutations and polymorphisms) needed to be identified in order to provide crit. clin. information concerning individual prognosis is considerably less than the 100,000 thought to comprise the human genome. The identification of the identity of the core group of genes enables the invention of a design for genetic profiling technologies which comprises of the identification of the core group of genes and their sequence variants required to provide a broad base of clin. prognostic information - "genostics". The "Genostic" profiling of patients and persons will radically enhance the ability of clinicians, healthcare professionals and other parties to plan and manage healthcare provision and the targeting of appropriate healthcare resources to those deemed most in need. The use of this invention could also lead to a host of new applications for such profiling technologies, such as identification of persons with particular work or

environment related risk, selection of applicants for employment, training or specific opportunities or for the enhancing of the planning and organization of health services, education services and social services.

IT **9001-91-6, Plasminogen 138757-15-0 139466-48-1 139639-23-9 140208-23-7 142243-03-6 148125-60-4**
RL: ANT (Analyte); THU (Therapeutic use); ANST (Analytical study); BIOL (Biological study); USES (Uses)
(core group of disease-related genes; gene probes used for genetic profiling in healthcare screening and planning)

L8 ANSWER 12 OF 29 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1999:795993 HCAPLUS
DOCUMENT NUMBER: 132:31743
TITLE: Gene probes used for genetic profiling in healthcare screening and planning
INVENTOR(S): Roberts, Gareth Wyn
PATENT ASSIGNEE(S): Genostic Pharma Limited, UK
SOURCE: PCT Int. Appl., 149 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9964626	A2	19991216	WO 1999-GB1779	19990604
W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
CA 2330929	AA	19991216	CA 1999-2330929	19990604
AU 9941586	A1	19991230	AU 1999-41586	19990604
AU 9941587	A1	19991230	AU 1999-41587	19990604
GB 2339200	A1	20000119	GB 1999-12914	19990604
GB 2339200	B2	20010912		
EP 1084273	A1	20010321	EP 1999-925207	19990604
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				

PRIORITY APPLN. INFO.:

GB 1998-12098	A	19980606
GB 1998-28289	A	19981223
GB 1998-16086	A	19980724
GB 1998-16921	A	19980805
GB 1998-17097	A	19980807
GB 1998-17200	A	19980808
GB 1998-17632	A	19980814
GB 1998-17943	A	19980819
WO 1999-GB1779	W	19990604

AB There is considerable evidence that significant factor underlying the individual variability in response to disease, therapy and prognosis lies in a person's genetic make-up. There have been

numerous examples relating that polymorphisms within a given gene can alter the functionality of the protein encoded by that gene thus leading to a variable physiol. response. In order to bring about the integration of genomics into medical practice and enable design and building of a technol. platform which will enable the everyday practice of mol. medicine a way must be invented for the DNA sequence data to be aligned with the identification of genes central to the induction, development, progression and outcome of disease or physiol. states of interest. According to the invention, the no. of genes and their configurations (mutations and polymorphisms) needed to be identified in order to provide crit. clin. information concerning individual prognosis is considerably less than the 100,000 thought to comprise the human genome. The identification of the identity of the core group of genes enables the invention of a design for genetic profiling technologies.

IT **9001-91-6, Plasminogen 138757-15-0 139466-48-1 139639-23-9 140208-23-7 142243-03-6 148125-60-4**
RL: ANT (Analyte); THU (Therapeutic use); ANST (Analytical study); BIOL (Biological study); USES (Uses)
(core group of disease-related genes; gene probes used for genetic profiling in healthcare screening and planning)

L8 ANSWER 13 OF 29 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1999:500754 HCAPLUS
DOCUMENT NUMBER: 132:87826
TITLE: Modulation of biological phenotypes for **tumor** growth and metastasis by target-specific biological inhibitors in gastric **cancer**
AUTHOR(S): Rha, Sun Young; Noh, Sung Hoon; Kim, Tae Soo; Yoo, Nae Choon; Roh, Jae Kyung; Min, Jin Sik; Kim, Byung Soo; Kim, Min Young; Chung, Hyun Cheol
CORPORATE SOURCE: Yonsei Cancer Research Institute, Yonesi Cancer Center, Department of Internal Medicine, Yonsei University College of Medicine, Seoul, 120-752, S. Korea
SOURCE: International Journal of Molecular Medicine (1999), 4(2), 203-212
CODEN: IJMMFG; ISSN: 1107-3756
PUBLISHER: International Journal of Molecular Medicine
DOCUMENT TYPE: Journal
LANGUAGE: English

AB For **tumor** progression, a cascade of linked sequential biol. events is essential. We tried to test whether biol. therapy can modulate specific biol. phenotypes and increase the anti-**tumor** effect when combined with chemotherapy. Five human gastric **cancer** cell lines (YCC-1, YCC-2, YCC-3, YCC-7, AGS) were used in these studies. Pentosan polysulfate (PPS) as a **heparin**-binding growth factor inhibitor, **Tranexamic** acid as a **plasmin** inhibitor, Lovastatin as an adhesion inhibitor and Adriamycin as a chemotherapeutic agent were selected. The effects of each drug on colony formation and **tumor** cell proliferation were evaluated by soft agar assay and cell proliferation assay, resp., to test direct anti-**tumor** effect. The expression of uPA and PAI-1 was detd. by ELISA, while MMPs activity was evaluated by zymog. PPS suppressed the

colony-forming activity as much as Adriamycin did, but it showed only cytostatic effects in cell proliferation assay. Migration capacity using Boyden chamber assay was more closely correlated with adhesive capacity than uPA or MMP-2 expression. The motility inhibitory effect of **Tranexamic** acid was obsd. in the YCC-7 cell line, which expressed all the required biol. phenotypes for migration. In AGS, with high cell motility and adhesiveness, the adhesion was inhibited by Lovastatin and most of the inhibitory effect was recovered by Mevalonate. When PPS was combined with Adriamycin on the Adriamycin-resistant, midkine (MK) gene expressing YCC-7 cell line, the growth inhibition rate increased up to 84%, while that for a single treatment of PPS or Adriamycin was 40% and 22%, resp. (p=0.001). When we combined **Tranexamic** acid and Adriamycin, we obsd. the synergistic effect in YCC-3 and YCC-7, while no combined effect was found in YCC-1. The combination of Lovastatin and Adriamycin did not show any combined effects in any of the cell lines. In conclusion, a synergistic anti-proliferative effect (chemo-sensitization) with combined chemo-biotherapy was found in **cancer** cells with specific biol. target, MK. The anti-motility effect was the greatest when the gastric **cancer** cells expressed all the specific biol. phenotypes.

IT **1197-18-8, Tranexamic** acid
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(modulation of biol. phenotypes for **tumor** growth and metastasis by target-specific biol. inhibitors in gastric **cancer**)

IT **140208-23-7, Plasminogen** activator inhibitor 1
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(modulation of biol. phenotypes for **tumor** growth and metastasis by target-specific biol. inhibitors in gastric **cancer**)

REFERENCE COUNT: 34 THERE ARE 34 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L8 ANSWER 14 OF 29 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1998:425304 HCAPLUS
DOCUMENT NUMBER: 129:213286
TITLE: Sp220K is a novel matrix serine proteinase
AUTHOR(S): Thaon, Sabine; Auberger, Patrick; Rossi, Bernard; Poustis-Delpont, Claudine
CORPORATE SOURCE: Laboratoire de Biochimie, Faculte de Medecine, Nice, Fr.
SOURCE: International Journal of Cancer (1998), 77(2), 264-270
CODEN: IJCNAW; ISSN: 0020-7136
PUBLISHER: Wiley-Liss, Inc.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Matrix proteinases play a crit. role in extracellular matrix remodeling, which is particularly involved in **cancer** invasion and metastasis. We have previously characterized and purified a new tetrameric serine proteinase (SP220K) from human kidney clear cell **carcinoma** plasma membranes. Here, we report that SP220K exhibits gelatinase activity as assessed both in

soln. and by zymog. Optimum gelatinase activity ranges between pH 7.5 to pH 9.0. Fibronectin and type I collagen were hydrolyzed by SP220K, at variance with laminin and type IV collagen. Like other trypsin-like fibronectin degrading proteinases, SP220K released the 29-kDa N-terminal **heparin**-binding domain of fibronectin. By using a panel of proteinase inhibitors, we found that the inhibition profile of SP220K was different from that of other known serine proteinases such as thrombin, trypsin, **plasmin**, **plasminogen** activators and tryptase. Altogether, our results indicate that SP220K corresponds to a novel matrix proteinase that exhibits a marked specificity for fibronectin and type I collagen.

REFERENCE COUNT: 22 THERE ARE 22 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L8 ANSWER 15 OF 29 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1998:239304 HCAPLUS
DOCUMENT NUMBER: 128:294008
TITLE: Fragments of **plasminogen** effective in inhibiting **tumor** metastasis and growth and process for preparing the same
INVENTOR(S): Morikawa, Wataru; Miyamoto, Seiji
PATENT ASSIGNEE(S): Juridical Foundation the Chemo-Sero-Therapeutic Research Institute, Japan; Morikawa, Wataru; Miyamoto, Seiji
SOURCE: PCT Int. Appl., 34 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: Japanese
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9815643	A1	19980416	WO 1997-JP3635	19971009
W: AU, CA, KR, US				
RW: AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
JP 10114796	A2	19980506	JP 1996-287651	19961009
AU 9745714	A1	19980505	AU 1997-45714	19971009
US 2002031518	A1	20020314	US 2001-989388	20011121

PRIORITY APPLN. INFO.:
JP 1996-287651 A 19961009
WO 1997-JP3635 W 19971009
US 1999-269720 A1 19990406

AB Fragments of a **plasminogen** effective in inhibiting **tumor** metastasis and growth, an enzymic process for prepg. the fragments, and a **tumor** metastasis and growth inhibitor contg. the fragments as the active ingredient are presented. The fragments are obtained from the elastase-induced hydrolysis product of Lys-**plasminogen** that is obtained by treating a **plasminogen** with **plasmin** and that preferably has a potent **heparin**-binding activity. Alternatively, the Lys-**plasminogen** is prepd. by autolysis of **plasminogen** in the presence of **tranexamic** acid. The inhibitor is useful for clin. therapy of solid **cancers** typified by lung and colon **cancers**.

IT **9005-49-6**, **Heparin**, biological studies

RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(Lys-**plasminogen** fragments binding to; fragments of **plasminogen** effective in inhibiting **tumor** metastasis and growth and process for prepg. same)

IT **9001-91-6**, Lys-**plasminogen**
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(de-(1-76) derivs.; fragments of **plasminogen** effective in inhibiting **tumor** metastasis and growth and process for prepg. same)

IT **1197-18-8**, **Tranexamic** acid
RL: BUU (Biological use, unclassified); BIOL (Biological study); USES (Uses)
(fragments of **plasminogen** effective in inhibiting **tumor** metastasis and growth and process for prepg. same)

REFERENCE COUNT: 5 THERE ARE 5 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L8 ANSWER 16 OF 29 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1998:174203 HCAPLUS
DOCUMENT NUMBER: 128:291355
TITLE: Sulfated glycosaminoglycans enhance **tumor** cell invasion in vitro by stimulating **plasminogen** activation
AUTHOR(S): Brunner, Georg; Reimbold, Karin; Meissauer, Andreas; Schirrmacher, Volker; Erkell, Lars J.
CORPORATE SOURCE: Division of Cellular Immunology, Tumor Immunology Program, German Cancer Research Centre, Heidelberg, Germany
SOURCE: Experimental Cell Research (1998), 239(2), 301-310
CODEN: ECREAL; ISSN: 0014-4827
PUBLISHER: Academic Press
DOCUMENT TYPE: Journal
LANGUAGE: English

AB We report here that the highly sulfated glycosaminoglycans, **heparin** and heparan sulfate, as well as the sulfated polysaccharide, fucoidan, significantly enhanced **tumor** cell invasion in vitro into fibrin, the basement membrane ext., Matrigel, or through a basement membrane-like extracellular matrix. The enhancement of **tumor** cell invasion was due to a stimulation of the proteolytic cascade of **plasminogen** activation since the effect required **plasminogen** activation and was abolished by inhibitors of urokinase-type **plasminogen** activator (uPA) or **plasmin**. Sulfated polysaccharides enhanced five reactions of **tumor**-cell initiated **plasminogen** activation in a dose-dependent manner. They amplified **plasminogen** activation in culture supernatants up to 70-fold by stimulating (1) pro-uPA activation by **plasmin** and (2) **plasminogen** activation by uPA. (3) In addn., sulfated polysaccharides partially protected **plasmin** from inactivation by .alpha.2-antiplasmin. Sulfated polysaccharides also stimulated **tumor**-cell assocd. **plasminogen** activation, e.g., (4) cell surface pro-uPA activation by **plasmin** and (5) **plasminogen** activation by cell surface uPA. These results suggest that sulfated

glycosaminoglycans liberated by **tumor**-cell mediated extracellular matrix degrdn. in vivo might amplify pericellular **plasminogen** activation and locally enhance **tumor** cell invasion in a pos. feedback manner.

IT **9005-49-6, Heparin,** biological studies
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(sulfated glycosaminoglycans enhance **tumor** cell invasion in vitro by stimulating **plasminogen** activation)

IT **9001-91-6, Plasminogen**
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(sulfated glycosaminoglycans enhance **tumor** cell invasion in vitro by stimulating **plasminogen** activation)

IT **105913-11-9, Plasminogen** activator
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(sulfated glycosaminoglycans enhance **tumor** cell invasion in vitro by stimulating **plasminogen** activation)

REFERENCE COUNT: 51 THERE ARE 51 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L8 ANSWER 17 OF 29 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1997:766891 HCAPLUS
DOCUMENT NUMBER: 128:97407
TITLE: Retinoic acid-enhanced invasion through reconstituted basement membrane by human SK-N-SH neuroblastoma cells involves membrane-associated tissue-type **plasminogen** activator
AUTHOR(S): Tiberio, Antonella; Farina, Antonietta R.; Tacconellii, Antonella; Cappabianca, Lucia; Gulino, Alberto; Mackay, Andrew R.
CORPORATE SOURCE: Section of Molecular Pathology, Departmnent of Experimental Medicine, University of L'Aquila, L'Aquila, 67100, Italy
SOURCE: International Journal of Cancer (1997), 73(5), 740-748
CODEN: IJCNAW; ISSN: 0020-7136
PUBLISHER: Wiley-Liss, Inc.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB AI-trans retinoic acid (RA) enhanced human, S-type, SK-N-SH neuroblastoma cell invasion of reconstituted basement membrane in vitro but did not induce terminal differentiation of this cell line. In contrast to basal invasion, which was urokinase (uPA)- and **plasmin**-dependent, RA-enhanced invasion was dependent on tissue-type **plasminogen** activator (t-PA) and **plasmin** activity. Neither basal nor RA-enhanced invasion involved TIMP-2 inhibitable metalloproteinases. Enhanced invasion was assocd. with the induction of t-PA expression, increased expression of the putative t-PA receptor amphoterin, increased assocn. of t-PA with cell membranes and increased net membrane-assocd. PA activity. Enhanced invasion was not assocd. with significant changes in the expression of uPA or its membrane receptor UPAR; **plasminogen** activator inhibitors PAI-1 and

PAI-2; metalloproteinases MMP-1, MMP-2, MMP-3, MMP-9 and membrane type MMP 1; or tissue inhibitors of metalloproteinases TIMP-1 and TIMP-2. RA stimulated the assocn. of t-PA with the external cell membrane surface, which could be inhibited by **heparin** sulfate but not by mannose sugars or chelators of divalent cations, consistent with a role for amphoterin. Our data indicate that RA can promote the malignant behavior of S-type neuroblastoma cells refractory to RA-mediated terminal differentiation by enhancing their basement membrane invasive capacity. We suggest that this results from the action of a novel, RA-regulated mechanism involving stimulation of t-PA expression and its assocn. with the cell membrane leading to increased PA-dependent matrix degrdn.

IT **139639-23-9**, Tissue-type **plasminogen** activator
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(tissue-type **plasminogen** activator in retinoic acid-enhanced invasion through neuroblastoma basement membrane)

L8 ANSWER 18 OF 29 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1997:447176 HCAPLUS
DOCUMENT NUMBER: 127:174398
TITLE: **Plasmin** and **plasminogen** activator inhibitor type 1 promote cellular motility by regulating the interaction between the urokinase receptor and vitronectin
AUTHOR(S): Waltz, David A.; Natkin, Lisa R.; Fujita, Ross M.; Wei, Ying; Chapman, Harold A.
CORPORATE SOURCE: Division Respiratory Diseases, Children's Hospital, Harvard Medical School, Boston, MA, 02115, USA
SOURCE: Journal of Clinical Investigation (1997), 100(1), 58-67
CODEN: JCINAO; ISSN: 0021-9738
PUBLISHER: Rockefeller University Press
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The urokinase receptor (uPAR) coordinates **plasmin**-mediated cell-surface proteolysis and promotes cellular adhesion via a binding site for vitronectin on uPAR. Because vitronectin also binds **plasminogen** activator inhibitor type 1 (PAI-1), and **plasmin** cleavage of vitronectin reduces PAI-1 binding, the authors explored the effects of **plasmin** and PAI-1 on the interaction between uPAR and vitronectin. PAI-1 blocked cellular binding of and adhesion to vitronectin by over 80% (IC50 .apprx. 5 nM), promoted detachment of uPAR-bearing cells from vitronectin, and increased cellular migration on vitronectin. Limited cleavage of vitronectin by **plasmin** also abolished cellular binding and adhesion and induced cellular detachment. A series of peptides surrounding a **plasmin** cleavage site (arginine 361) near the carboxy-terminal end of vitronectin were synthesized. Two peptides spanning res 364-380 blocked binding of uPAR to vitronectin (IC50 .apprx. 8-25 .mu.M) identifying this region as an important site of uPAR-vitronectin interaction. These data illuminate a complex regulatory scheme for uPAR-dependent cellular adhesion to vitronectin: active urokinase promotes adhesion and also subsequent detachment through activation of **plasmin** or complex formation with PAI-1. Excess PAI-1 may also promote migration by blocking cellular adhesion and/or promoting detachment, possibly

accounting in part for the strong correlation between PAI-1 expression and **tumor** cell metastasis.

IT **140208-23-7**, **Plasminogen** activator inhibitor type 1
RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(interactions of urokinase receptor and vitronectin are regulation by components of the urokinase-type **plasminogen** activator/**plasmin** system)

L8 ANSWER 19 OF 29 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1997:384287 HCAPLUS
DOCUMENT NUMBER: 127:1228
TITLE: Angiotensin IV and analogs as regulators of fibrinolysis
INVENTOR(S): Vaughan, Douglas E.; Harding, Joseph W.
PATENT ASSIGNEE(S): Brigham and Women's Hospital, USA; Washington State University Research Foundation
SOURCE: PCT Int. Appl., 64 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9716201	A1	19970509	WO 1996-US13804	19960827
W: AU, CA, JP				
RW: AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
AU 9668617	A1	19970522	AU 1996-68617	19960827
PRIORITY APPLN. INFO.:			US 1995-550174	19951030
			WO 1996-US13804	19960827

AB Angiotensin IV (VAL-TYR-ILE-HIS-PRO-PHE), a degrdn. product of angiotensin II previously thought to be inactive, interacts directly with endothelial cells to induce expression of PAI-1 and thereby to inhibit clot lysis attributable to endogenous t-PA. Moreover, angiotensin IV does not effect substantial physiol. changes (vasoconstriction, increased blood pressure, etc.) characteristic of angiotensin II. Fibrinolysis is promoted by reducing the amt. or the effect of angiotensin IV. Fibrinolysis is inhibited by providing enhanced angiotensin IV. Methods of screening candidates for antagonizing angiotensin IV are also disclosed.

IT **139639-23-9**, Tissue **plasminogen** activator
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(angiotensin IV inhibits clot lysis attributable to t-PA by interacting with endothelial cells to induce expression of PAI-1 fibrinolysis)

IT **140208-23-7**
RL: BSU (Biological study, unclassified); MFM (Metabolic formation); BIOL (Biological study); FORM (Formation, nonpreparative)
(angiotensin IV inhibits clot lysis attributable to t-PA by interacting with endothelial cells to induce expression of PAI-1 fibrinolysis)

IT **105913-11-9**, **Plasminogen** activator

RL: BOC (Biological occurrence); BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); OCCU (Occurrence); PROC (Process)
(defective release or diminished venous content; angiotensin IV and analogs as promoters or inhibitors of fibrinolysis in a variety of medical conditions)

IT **105844-41-5**, PAI
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(excessive release; angiotensin IV and analogs as promoters or inhibitors of fibrinolysis in a variety of medical conditions)

L8 ANSWER 20 OF 29 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1997:337128 HCAPLUS
DOCUMENT NUMBER: 127:16116
TITLE: Upregulation of urokinase-type **plasminogen** activator by endogenous and exogenous HIV-1 Tat protein in **tumor** cell lines derived from BK virus/tat-transgenic mice
AUTHOR(S): Rusnati, Marco; Coltrini, Daniela; Campioni, Diana; Tanghetti, Elena; Corallini, Alfredo; Barbanti-Brodano, Giuseppe; Giuliani, Roberta; Gibellini, Davide; Presta, Marco
CORPORATE SOURCE: Department of Biomedical Sciences and Biotechnology, Chair of General Pathology and Immunology, University of Brescia, Brescia, 25123, Italy
SOURCE: AIDS (London) (1997), 11(6), 727-736
CODEN: AIDSET; ISSN: 0269-9370
PUBLISHER: Rapid Science Publishers
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The authors demonstrate that Tat modulates the **plasminogen** -dependent proteolytic activity of **tumor** cell lines derived from BK virus (BKV)/tat-transgenic mice by affecting the prodn. of **plasminogen** activators (PA) and the PA inhibitor (PAI)-1 and demonstrate that this occurs through mechanism(s) that are distinct from those responsible for transactivating activity of extracellular Tat. The authors assessed whether endogenous Tat is responsible for PA activity in T53 adenocarcinoma cells, cell cultures were transfected with antisense Tat cDNA and evaluated for cell-assocd. PA activity by a **plasmin** chromogenic assay. The assay was also used to evaluate PA activity in T53 cells and T111 leiomyosarcoma cells stimulated by extracellular Tat. The type(s) of PA produced were identified by SDS-PAGE zymog. The levels of PAI-1 were evaluated by Western blotting. Tat transactivating activity was measured by a chloramphenicol acetyltransferase (CAT) ELISA in HL3T1 cells contg. integrated copies of an HIV-1 long terminal repeat (LTR)-CAT plasmid. Transfection of T53 cells with antisense Tat cDNA results in the decrease of Tat prodn. and PA activity. Exogenously added Tat increases PA levels in T53 and in T111 cells. PA activity was identified as urokinase-type PA (uPA). Tat also increases the prodn. of PAI-1 in T111 but not in T53 cells. Chloroquine and **heparin** have different affects on the LTR-CAT-transactivating and the PA-inducing activities of Tat. The fusion protein glutathione-S-transferase-Tat and the mutant Tat-1e, lacking

the second Tat exon, cause LTR-CAT transactivation without stimulating uPA upregulation. Tat affects the fibrinolytic activity of **tumor** cell lines derived from BKV/tat-transgenic mice by modulating the prodn. of both uPA and PAI-1 via autocrine and paracrine mechanisms of action. The capacity of Tat to modulate the **plasminogen**-dependent proteolytic activity of these **tumor** cell lines may contribute to their metastatic potential. The uPA-inducing activity of Tat depends upon specific biol. and structural features of the Tat protein that are distinct from those responsible for its LTR-CAT-transactivating activity, suggesting distinct mechanisms of induction for the two biol. responses.

IT **140208-23-7**, **Plasminogen** activator inhibitor 1
RL: BSU (Biological study, unclassified); MFM (Metabolic formation); BIOL (Biological study); FORM (Formation, nonpreparative)
(urokinase-type **plasminogen** activator upregulation by HIV-1 Tat protein in transgenic **tumor** cells)

L8 ANSWER 21 OF 29 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1997:18359 HCAPLUS
DOCUMENT NUMBER: 126:42690
TITLE: Inhibitors of fibrin crosslinking and/or transglutaminases
INVENTOR(S): Sawyer, Roy T.; Wallis, Robert B.; Seale, Lisa; Finney, Sarah
PATENT ASSIGNEE(S): Biopharm Research and Development Limited, UK; Sawyer, Roy T.; Wallis, Robert B.; Seale, Lisa; Finney, Sarah
SOURCE: PCT Int. Appl., 39 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9634890	A2	19961107	WO 1996-GB1093	19960507
WO 9634890	A3	19971023		
W: AL, AM, AT, AU, AZ, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IS, JP, KE, KG, KP, KR, KZ, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI				
RW: KE, LS, MW, SD, SZ, UG, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN				
CA 2220268	AA	19961107	CA 1996-2220268	19960507
AU 9656546	A1	19961121	AU 1996-56546	19960507
AU 723130	B2	20000817		
EP 848719	A2	19980624	EP 1996-913623	19960507
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				
CN 1187201	A	19980708	CN 1996-194644	19960507
JP 11505218	T2	19990518	JP 1996-533139	19960507
BR 9608207	A	20001031	BR 1996-8207	19960507
NO 9705080	A	19980102	NO 1997-5080	19971104
US 6025330	A	20000215	US 1998-945998	19980514

PRIORITY APPLN. INFO.: GB 1995-9271 A 19950505

WO 1996-GB1093 W 19960507

OTHER SOURCE(S): MARPAT 126:42690

AB A polypeptide (Tridegin) of mol. wt. of .apprx. 7000-8000 daltons, which inhibits transglutaminase activity and/or fibrin crosslinking, is isolated from tissue or secretions of the leech of the order Rhynchobdellida and purified by chromatog. methods. Because of extreme potency of polypeptides in the nanomolar range, they can be used to treat a no. of diseases where protein crosslinking is important, such as thromboembolic disease. They can be used for the treatment of Crohn's disease, **tumor** implantation, atherosclerosis, thrombotic microangiopathy, fibrous growths of the skin, acne, scar formation, membranous glomerulonephritis, cataracts, or infection with microfilarial nematodes. In particular, they can be used to reduce the stability of thrombi so that they are more susceptible to lysis by thrombolytic agents.

IT **9005-49-6**, **Heparin**, biological studies
139639-23-9, Tissue **plasminogen** activator
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(polypeptides from leech as inhibitors of fibrin crosslinking and/or transglutaminase activity)

L8 ANSWER 22 OF 29 HCAPLUS COPYRIGHT 2003 ACS

ACCESSION NUMBER: 1993:514576 HCAPLUS

DOCUMENT NUMBER: 119:114576

TITLE: Amphoterin, the 30-kDa protein in a family of HMG1-type polypeptides. Enhanced expression in transformed cells, leading edge localization, and interactions with **plasminogen** activation

AUTHOR(S): Parkkinen, Jaakko; Raulo, Erkki; Merenmies, Jussi; Nolo, Riitta; Kajander, E. Olavi; Baumann, Marc; Rauvala, Heikki

CORPORATE SOURCE: Dep. Med. Chem., Univ. Helsinki, Helsinki, Finland

SOURCE: Journal of Biological Chemistry (1993), 268(26), 19726-38
CODEN: JBCHA3; ISSN: 0021-9258

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Amphoterin is a **heparin**-binding protein that is developmentally regulated in brain and functionally involved in neurite outgrowth. Unexpectedly, amphoterin has a high mobility group 1 (HMG1)-type sequence. In the present study the authors have expressed amphoterin cDNA in a baculovirus vector and produced antibodies against the recombinant protein and several synthetic peptides. It was found that the amphoterin cDNA encodes the 30-kDa form of the protein isolated from tissues, whereas the co-purifying 28- and 29-kDa proteins (p28 and p29) have closely related but distinct primary structures. Partial amino acid sequencing shows several local changes in the sequences of p28 and p29 as compared to amphoterin, suggesting the occurrence of a multigene family that encodes at least three different HMG1-type sequences in the rat. Studies using the probes that discern amphoterin from the other HMG1-type proteins indicate a high level expression in various transformed cell lines. Immunostaining of cells with the amphoterin-specific antibodies indicates a cytoplasmic localization that becomes remarkably enriched at the leading edges in spreading and motile cells. An extracellular localization is suggested by

immunostaining of non-permeabilized cells and by a **plasminogen**-dependent degrdn. of amphoterin in the substratum-attached material of cells. Tissue-derived and recombinant amphoterins strongly enhance the rate of **plasminogen** activation and promote the generation of surface-bound **plasmin** both by tissue-type and urokinase-type **plasminogen** activators. The results suggest an extracellular function for amphoterin in the leading edge of various invasive cells.

IT **9001-91-6, Plasminogen**
RL: PROC (Process)
(amphoterin activation of, in **neoplastic** cells, invasive growth in relation to)

IT **139639-23-9**, Tissue-type **plasminogen** activator
RL: BIOL (Biological study)
(**plasmin** formation by, amphoterin promotion of, in **neoplastic** cells, invasive growth in relation to)

L8 ANSWER 23 OF 29 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1991:670331 HCAPLUS
DOCUMENT NUMBER: 115:270331
TITLE: Inhibition of **tumor** implantation at sites of trauma by **plasminogen** activators
AUTHOR(S): Murthy, M. Satya; Summaria, Louis J.; Miller, Richard J.; Wyse, Tamara B.; Goldschmidt, Robert A.; Scanlon, Edward F.
CORPORATE SOURCE: Dep. Med., Evanston Hosp., Evanston, IL, USA
SOURCE: Cancer (New York, NY, United States) (1991), 68(8), 1724-30
CODEN: CANCAR; ISSN: 0008-543X
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The authors report on the influence of **plasminogen** activators (PA) on implantation of TA3Ha mammary **tumor** cells in the healing hepatic wounds of syngeneic strain A mice. I.v. injected TA3Ha cells, although they rarely metastasize to the liver, formed **tumors** in the hepatic wounds (42%) of mice. The frequency of **tumor** formation declined as the interval between surgery and **tumor** cell inoculation was increased. Furthermore, preexposure of cells to fibrinogen, fibronectin, laminin, or peptides contg. the arginine-glycine-aspartic acid-serine residues dramatically reduced the frequency of **tumor** formation in the hepatic wounds. These results indicate that TA3Ha cells interact with fibrinogen-related proteins in the wound to aid their attachment and growth. Because these proteins are susceptible to digestion by **plasmin**, PA were used in this study to examine whether administration of these drugs to the mice would modulate **tumor** formation in the liver wounds. Among the PA tested, human **plasmin** B-chain-streptokinase complex (B-SK) and recombinant tissue **plasminogen** activator (t-PA) inhibited **tumor** implantation in a dose-related manner. Administration of 900 units (U) of B-SK or 3300 U ot t-PA per mouse reduced the frequency of **tumor** formation from 42% to 0% and 11%, resp. The B-SK was complexed with p-nitrophenyl p-guanidinobenzoate; it did not activate the **plasminogen** or inhibit **tumor** formation in the hepatic wounds. Although urokinase activated the

plasminogen, it did not inhibit **tumor** implantation in the hepatic wound. **Heparin**, an anticoagulant that prevents conversion of fibrinogen to fibrin without being fibrinolytic, had no influence on **tumor** formation in the hepatic wounds. The PA can generate **plasmin** that digests the cell attachment proteins in wounds and consequently inhibits **tumor** cell attachment.

IT **105913-11-9, Plasminogen** activator
RL: BIOL (Biological study)
(recombinant tissue-type, **tumor** implantation at sites of liver injury inhibition by)

IT **9005-49-6, Heparin**, biological studies
RL: BIOL (Biological study)
(**tumor** implantation at sites of liver injury inhibition by)

L8 ANSWER 24 OF 29 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1989:624923 HCAPLUS
DOCUMENT NUMBER: 111:224923
TITLE: Effects of various chemical compounds on Ehrlich ascites **tumor** cells in a maintenance medium
AUTHOR(S): Takamura, Shozo; Yoshida, Junko; Suzuki, Shiro
CORPORATE SOURCE: Dep. Pharmacol., Kanazawa Med. Univ., Uchinada, 920-02, Japan
SOURCE: Kanazawa Ika Daigaku Zasshi (1989), 14(2), 241-5
CODEN: KIDZDN; ISSN: 0385-5759
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The effects of 71 natural and synthetic chem. compds. on Ehrlich ascites **tumor** cells in a maintenance medium were examd. Nine thiols and related compds. promoted the cell growth. Fifteen potent cytotoxic compds. were tested at lower concns. against the same cells. Two of these compds., diethyldithiocarbamate and menadione, showed a marked cell-killing effect. Their mechanisms of cytotoxic action are discussed.

IT **1197-18-8, Tranexamic** acid **9001-91-6, Plasminogen 9005-49-6, Heparin**, biological studies
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(**neoplasm** inhibition by)

L8 ANSWER 25 OF 29 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1988:487008 HCAPLUS
DOCUMENT NUMBER: 109:87008
TITLE: Further characterization of malignant glioma-derived vascular permeability factor
AUTHOR(S): Criscuolo, Gregory R.; Merrill, Marsha J.; Oldfield, Edward H.
CORPORATE SOURCE: Natl. Inst. Neurol., Natl. Inst. Health, Bethesda, MD, USA
SOURCE: Journal of Neurosurgery (1988), 69(2), 254-62
CODEN: JONSAC; ISSN: 0022-3085
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The nature of vascular permeability factor (VPF) activity derived

from serum-free conditioned medium contg. cultured human malignant glial **tumors** was investigated further. A 1000-fold purifn. was accomplished by sequential **heparin**-Sepharose affinity chromatog. and HPLC gel filtration chromatog. steps. Vascular permeability factor activity falls into the mol. wt. range 41,000-56,000 daltons. Activity is bound to hydroxylapatite, carboxymethyl-Sepharose, phenyl-Sepharose, and **heparin** -Sepharose, whereas little or no activity is bound to DEAE-Sephacel. Vascular permeability factor activity is trypsin- and pepsin-sensitive but is unaffected by treatment with RNase A. This suggests that VPF is a hydrophobic, pos. charged (cationic) polypeptide with a potentially biol. significant affinity for **heparin**. As most proteins are neg. charged (anionic) and have no affinity for **heparin**, an advantage was gained by performing these purifn. steps. The activity of VPF is not inhibited by coinjection of conditioned medium with soybean trypsin inhibitor or hexadimethrine (both known antagonists of tissue **plasminogen** activator, Hageman factor, and serum kallikrein), with aprotinin (an antagonist of both **plasmin** and tissue kallikrein), with phenylmethanesulfonyl fluoride (a serine esterase (elastase) inhibitor), or with pepstatin-A (an acid protease inhibitor which inactivates vascular permeability-inducing leukokinins). These data, together with the fact that VPF is produced and released into serum-free media, provide substantial evidence against it being one of the more commonly known serum-derived permeability mediators. Treatment with dithiothreitol inhibits VPF activity, indicating the presence of at least 1 essential disulfide bond in this mol. Inhibition by dexamethasone of VPF expression in cultured malignant glial cells appears to be selective. Dexamethasone-induced inhibition of VPF is dose-responsive and is not assocd. with a parallel inhibition of cellular protein synthesis as detd. by [3H]leucine incorporation into TCA-precipitable material. Inclusion of dexamethasone in the culture medium is not assocd. with altered cell viability or cell no. In vivo studies confirm the inhibition of VPF activity in test animals pretreated with dexamethasone. This steroid-induced inhibition is partially reversed by treatment of test animals with actinomycin D prior to exposure to dexamethasone. The latter finding suggests that dexamethasone exerts its inhibitory action by induction of de novo protein synthesis.

L8 ANSWER 26 OF 29 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1988:453028 HCAPLUS
DOCUMENT NUMBER: 109:53028
TITLE: **Plasminogen** activator release from cultured murine mast cells
AUTHOR(S): Bartholomew, Jennifer S.; Woolley, David E.
CORPORATE SOURCE: Dep. Med., Univ. Hosp. South Manchester, West Didsbury/Manchester, M20 8LR, UK
SOURCE: Biochemical and Biophysical Research Communications (1988), 153(2), 540-4
CODEN: BBRCA9; ISSN: 0006-291X
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Mast cells from the Furth murine mastocytoma **tumor** line were found to contain significant levels of **plasminogen** activator (PA). Cultured cells released PA activity into the culture medium in parallel with the release of histamine, and both

were proportionately increased following exposure to degranulating agents. Pretreatment of the mast cells with cycloheximide did not alter their total PA content or their ability to release PA. Apparently, PA is a prestored granule constituent. The ability of PA to generate **plasmin** from **plasminogen** suggests an important role for mast cell PA in fibrinolysis and tissue degrdn., observations that have been assocd. with mast cell degranulation and infiltration in vivo.

IT **9005-49-6, Heparin**, biological studies
RL: BIOL (Biological study)
(of mast cell, **plasminogen** activator in relation to)

IT **105913-11-9, Plasminogen** activator
RL: PROC (Process)
(release of, from mast cell granule)

L8 ANSWER 27 OF 29 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1984:65652 HCAPLUS
DOCUMENT NUMBER: 100:65652
TITLE: Evidence that a variety of cultured cells secrete protease-nexin and produce a distinct cytoplasmic serine protease-binding factor
AUTHOR(S): Eaton, Dan L.; Baker, Joffre B.
CORPORATE SOURCE: Dep. Biochem., Univ. Kansas, Lawrence, KS, USA
SOURCE: Journal of Cellular Physiology (1983), 117(2), 175-82
CODEN: JCLLAX; ISSN: 0021-9541
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Four criteria were used to examine serum-free conditioned cell culture medium for protease-nexin (PN): formation of SDS-stable .apprx.77 kilodalton (kDa) complexes between a medium component and 125I-labeled thrombin; acceleration by **heparin** of the rate of formation of these complexes; cellular binding of these complexes; and **heparin** inhibition of the cellular binding of complexes. PN was detected in media from the following cell types: human foreskin fibroblasts (HF cells) (0.18 .mu.g PN/106 cells), rat embryo heart muscle cells (0.13 .mu.g/106 cells), mouse myotubules (0.1 .mu.g/106 cells), monkey kidney epithelial cells, human fibrosarcoma cells, human lung fibroblasts (WI-26 cells), SV-40 virus-transformed human fibroblasts, human epidermoid **carcinoma** cells, bovine aortic endothelial cells (only after phorbol ester treatment), and mouse myoblasts. No PN was found in medium conditioned by mouse 3T3 cells, SV40 virus-transformed 3T3 cells, human lymphoblasts, or mouse leukemia cells. Eleven of the cell types examd. for secretion of PN were examd. for the presence of cytoplasmic thrombin-binding factors and found to contain a factor that formed .apprx.60-65 kDa SDS-stable complexes with 125I-labeled thrombin. These complexes are significantly smaller than the thrombin-PN complexes, indicating that the cytoplasmic factor is distinct from PN. Nevertheless, PN and the cytoplasmic factor share similarities. Prodn. of both PN (by HF cells and WI-26 cells) and the cytoplasmic factor (by HF cells and 3T3 cells) are stimulated by epidermal growth factor and phorbol myristate acetate. Also, both PN and the cytoplasmic factor form complexes with trypsin, **plasmin**, urokinase, and thrombin, but not with pancreatic elastase. Because a no. of the cells that produce PN or the cytoplasmic serine protease-binding factor produce **plasminogen** activators, both PN and the cytoplasmic factor

could regulate **plasminogen** activator activity.

IT **148263-58-5**
RL: BIOL (Biological study)
(formation and secretion of, by human and lab. animal cells, epidermal growth factor and phorbol myristate acetate stimulation of, cytoplasmic proteinase-binding factor in relation to)

L8 ANSWER 28 OF 29 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1982:444308 HCAPLUS
DOCUMENT NUMBER: 97:44308
TITLE: Preparation of **antitumor** cold-insoluble globulins from blood plasma
PATENT ASSIGNEE(S): Haranaka, Katsumasa, Japan
SOURCE: Jpn. Kokai Tokkyo Koho, 3 pp.
CODEN: JKXXAF
DOCUMENT TYPE: Patent
LANGUAGE: Japanese
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
JP 57067520	A2	19820424	JP 1980-142578	19801013

PRIORITY APPLN. INFO.: JP 1980-142578 19801013

AB Cold-insol. globulins are isolated as **neoplasm** inhibitors from human blood plasma. The blood plasma was treated with **heparin** and the cells were removed by centrifugation. The supernatant was frozen, thawed, and centrifuged at 3000 rpm at 4.degree. for 20 min to obtain a ppt. The ppt. was dissolved in saline and the freezing-thawing process was repeated. Finally, the dissolved ppt. was chromatographed to remove **plasmins** and **plasminogens** and to obtain a **tumor**-inhibiting material.

L8 ANSWER 29 OF 29 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1977:187328 HCAPLUS
DOCUMENT NUMBER: 86:187328
TITLE: The extract from the tissue of gastric **cancer** as procoagulant in disseminated intravascular coagulation syndrome
AUTHOR(S): Sakuragawa, Nobuo; Takahashi, Kaoru; Hoshiyama, Mari; Jimbo, Chozo; Ashizawa, Ken; Matsuoka, Matsuzo; Ohnishi, Yoshihusa
CORPORATE SOURCE: Sch. Med., Niigata Univ., Niigata, Japan
SOURCE: Thrombosis Research (1977), 10(3), 457-63
CODEN: THBRAA; ISSN: 0049-3848
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Tissue exts. from 2 histopathol. types of surgically removed gastric **cancer** were investigated for procoagulant and fibrinolytic activities. Procoagulant activity was due to a thromboplastin-like substance; 1 mg of the ext. protein was equiv. to 0.014 mg of Lyoplastin (thromboplastin). It was inhibited by **heparin**, Trasylol and was partially inactivated by heating at 100.degree. for 10 min, but not at 56.degree.C and 37.degree.. The exts. had both **plasminogen** activator and **plasmin** activities. The fibrinolytic activity was inhibited by soybean trypsin inhibitor, Trasylol, and trans-aminomethylhexan-carboxylic acid. In 12 cases

studied, 9 were of adenocarcinoma and 3 were **carcinoma** simplex. Both procoagulant and fibrinolytic activities appeared to be greatest in the exts. from adenocarcinoma, as compared to those from **carcinoma** simplex or the normal tissue surrounding the lesions.

(FILE 'MEDLINE, BIOSIS, EMBASE, WPIDS, CONFSCI, SCISEARCH, JICST-EPLUS, JAPIO, CANCERLIT' ENTERED AT 15:15:56 ON 26 JUN 2003)
L9 100 S L8
L10 56 DUP REM L9 (44 DUPLICATES REMOVED)

L10 ANSWER 1 OF 56 WPIDS (C) 2003 THOMSON DERWENT
ACCESSION NUMBER: 2002-750514 [81] WPIDS
DOC. NO. NON-CPI: N2002-591081
DOC. NO. CPI: C2002-212685
TITLE: Medical stent useful for treatment of stenosed vasculature or other body passages having a coating comprising a primer layer comprising a first composition and drug reservoir layer comprising second composition.
DERWENT CLASS: A96 B05 B07 D16 D22 P32
INVENTOR(S): CALISTRI-YEH, M; CHAMBERLAIN, A M; HULLIHEN, D G; ROSEBROUGH, S F; WHITBOURNE, R J
PATENT ASSIGNEE(S): (STSB-N) STS BIOPOLYMERS INC
COUNTRY COUNT: 100
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
WO 2002074194	A2	20020926	(200281)*	EN	45

RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW MZ NL OA PT SD SE SL SZ TR TZ UG ZM ZW
W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU CZ DE DK DM DZ EC EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ OM PH PL PT RO RU SD SE SG SI SK SL TJ TM TN TR TT TZ UA UG US UZ VN YU ZA ZM ZW

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
WO 2002074194	A2	WO 2002-US8039	20020318

PRIORITY APPLN. INFO: US 2001-276089P 20010316
AN 2002-750514 [81] WPIDS
AB WO 200274194 A UPAB: 20021216
NOVELTY - Medicated stent (S1) with a coating comprising a primer layer (a) comprising a first composition (a1) of at least one polymer, and a drug reservoir layer (b) comprising a second composition (b1) of at least one polymer and active agent(s). The coating remains intact upon stent expansion and releases drug at site of expansion.
DETAILED DESCRIPTION - INDEPENDENT CLAIMS are included for the following:
(1) Preparation of the medicated stent (S1) by
(1) either applying a primer polymer liquid comprising at least

one polymer in a volatile medium, applying a drug reservoir polymer liquid comprising at least one polymer in a volatile medium, applying an active agent either together with or after applying the drug reservoir polymer liquid and removing the volatile media; or

(2) applying (a) and (b) comprising at least two polymers and at least one active agent; and

(2) Administration of a bioactive agent to a target site in a subject involving implanting S1 at the target site of the subject and expanding to allow active agent to elute from the coating during an extended period;

ACTIVITY - Vasotropic; Anticoagulant; Thrombolytic.

MECHANISM OF ACTION - None given in source document.

USE - For administering a bioactive agent to a target site in a subject (claimed) and for the treatment of stenosed vasculature or other body passages.

ADVANTAGE - The stent provides therapeutic activity from the surfaces of stents in order to reduce the incidence of restenosis and thrombus formation after coronary stenting procedures in the clinic. The polymer layers possess excellent flexibility and elasticity and are expandable. The polymers are not bioerodable such that differences in hormonal activity from patient to patient are minimized. The polymer layer provides reservoirs for a variety of drugs or drug cocktails.

Dwg.0/1

L10 ANSWER 2 OF 56 MEDLINE DUPLICATE 1

ACCESSION NUMBER: 2002709220 MEDLINE

DOCUMENT NUMBER: 22359098 PubMed ID: 12381729

TITLE: A truncated **plasminogen** activator inhibitor-1 protein blocks the availability of **heparin**-binding vascular endothelial growth factor A isoforms.

AUTHOR: Mulligan-Kehoe Mary Jo; Kleinman Hynda K; Drinane Mary; Wagner Robert J; Wieland Courtney; Powell Richard J

CORPORATE SOURCE: Department of Surgery, Vascular Surgery Section, Dartmouth Medical School, Dartmouth College, Hanover, New Hampshire 03756, USA.. mary.j.mulligan-kehoe@dartmouth.edu

CONTRACT NUMBER: R01-HL59590 (NHLBI)

SOURCE: JOURNAL OF BIOLOGICAL CHEMISTRY, (2002 Dec 13) 277 (50) 49077-89.
Journal code: 2985121R. ISSN: 0021-9258.

PUB. COUNTRY: United States

DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)

LANGUAGE: English

FILE SEGMENT: Priority Journals

ENTRY MONTH: 200301

ENTRY DATE: Entered STN: 20021217
Last Updated on STN: 20030129
Entered Medline: 20030128

AB We have made deletions of the porcine **plasminogen** activator inhibitor-1 (PAI-1) gene to obtain recombinant truncated PAI-1 proteins to examine functions of the PAI-1 isoforms. We previously reported that one recombinant truncated protein, rPAI-1(23), induces the formation of angiostatin by cleaving **plasmin**. The rPAI-1(23) protein is also able to bind urokinase **plasminogen** activator and **plasminogen**

and then reduce the amount of **plasmin** that is formed. We have now prepared three different truncated rPAI-1 proteins and demonstrate that PAI-1 conformations control the release of **heparin**-binding vascular endothelial growth factor (VEGF) isoforms. The rPAI-1(23) isoform can regulate the functional activity of heparan sulfate-binding VEGF-A isoforms by blocking the activation of VEGF from heparan sulfate. The rPAI-1(23) conformation induced extensive apoptosis in cultured endothelial cells and thus reduced the number of proliferating cells. The rPAI-1(23) isoform inhibited migration of VEGF-stimulated sprouting from chick aortic rings by 65%, thus displaying a role in anti-angiogenic mechanisms. This insight into anti-angiogenic functions related to PAI-1 conformational changes could provide potential intervention points in angiogenesis associated with atherosclerotic plaques and **cancer**.

L10 ANSWER 3 OF 56 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 2002088506 EMBASE
TITLE: Treatment of malignancy by activation of the **plasminogen** system.
AUTHOR: Zacharski L.R.; Ornstein D.L.; Gabazza E.C.; D'Alessandro-Gabazza C.N.; Brugarolas A.; Schneider J.
CORPORATE SOURCE: Dr. L.R. Zacharski, VA Medical/Regional Office Center, 215 N. Main Street, White River Junction, VT 05009, United States. leo.r.zacharski@dartmouth.edu
SOURCE: Seminars in Thrombosis and Hemostasis, (2002) 28/1 (5-17).
Refs: 121
ISSN: 0094-6176 CODEN: STHMBV
COUNTRY: United States
DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 016 Cancer
030 Pharmacology
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English
AB The blood coagulation mechanism in general and the **plasminogen** system in particular contribute to malignant growth and dissemination in complex ways. This article reviews the extensive literature that has accumulated over the past half-century on effects of **plasminogen** activation on the natural history of experimental animal and human malignancy. Although the potent enzymes generated upon **plasminogen** activation may have a direct effect on **tumor** cells, it is more likely that their mechanism of action is related to disruption of the **tumor** cell-extracellular matrix interaction. These observations suggest novel approaches to the experimental therapy of **cancer**.

L10 ANSWER 4 OF 56 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 2002106658 EMBASE
TITLE: Phage display as a tool for protease ligand discovery.
AUTHOR: Nixon A.E.
CORPORATE SOURCE: A.E. Nixon, Dyax Corp., One Kendall Square, Cambridge, MA 02139, United States. anixon@dyax.com
SOURCE: Current Pharmaceutical Biotechnology, (2002) 3/1

(1-12).
Refs: 115
ISSN: 1389-2010 CODEN: CPBUBP
COUNTRY: Netherlands
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 016 Cancer
025 Hematology
029 Clinical Biochemistry
037 Drug Literature Index
052 Toxicology
LANGUAGE: English
SUMMARY LANGUAGE: English
AB Proteolytic enzymes have been implicated as the pathological agent in a number of disease states. For this reason proteases are attractive therapeutic targets. Phage display of peptide libraries can be used to identify peptides that may be used either directly as inhibitors or serve as leads in the generation of prodrugs and peptidomimetics.

L10 ANSWER 5 OF 56 WPIDS (C) 2003 THOMSON DERWENT
ACCESSION NUMBER: 2001-529979 [58] WPIDS
DOC. NO. CPI: C2001-158124
TITLE: Proteinaceous molecule, useful for treating diseases related with angiogenesis, inflammatory, conformational disorders and ageing, comprises lysine and/or arginine residues and is capable of providing enhanced levels of **plasmin**.
DERWENT CLASS: B04 D16
INVENTOR(S): GEBBINK, M F B G; VOEST, E E
PATENT ASSIGNEE(S): (UYUT-N) RIJKSUNIV UTRECHT; (UYUT-N) UNIV UTRECHT MEDISCH CENT; (GEBB-I) GEBBINK M F B G; (VOES-I) VOEST E E
COUNTRY COUNT: 95
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
WO 2001062799	A2	20010830	(200158)*	EN	29
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW MZ NL OA PT SD SE SL SZ TR TZ UG ZW					
W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CR CU CZ DE DK DM DZ EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT TZ UA UG US UZ VN YU ZA ZW					
EP 1130031	A1	20010905	(200159)	EN	
R: AL AT BE CH CY DE DK ES FI FR GB GR IE IT LI LT LU LV MC MK NL PT RO SE SI					
AU 2001041262	A	20010903	(200202)		
EP 1257582	A2	20021120	(200301)	EN	
R: AL AT BE CH CY DE DK ES FI FR GB GR IE IT LI LT LU LV MC MK NL PT RO SE SI TR					
US 2003050245	A1	20030313	(200321)		

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE

WO 2001062799 A2	WO 2001-NL155	20010226
EP 1130031 A1	EP 2000-200664	20000225
AU 2001041262 A	AU 2001-41262	20010226
EP 1257582 A2	EP 2001-912573	20010226
	WO 2001-NL155	20010226
US 2003050245 A1 Cont of	WO 2001-NL155	20010226
	US 2002-229394	20020826

FILING DETAILS:

PATENT NO KIND		PATENT NO
AU 2001041262 A	Based on	WO 200162799
EP 1257582 A2	Based on	WO 200162799

PRIORITY APPLN. INFO: EP 2000-200664 20000225
AN 2001-529979 [58] WPIDS
AB WO 200162799 A UPAB: 20011010
NOVELTY - A proteinaceous molecule (I) which is at least in vitro a cofactor of tissue **plasminogen** activator (tPA) comprising a lysine and/or arginine residue and/or its functional equivalent, capable of providing enhanced levels of **plasmin** in a mammal through tPA mediated **plasminogen** activation for use as a pharmaceutical, is new.

DETAILED DESCRIPTION - INDEPENDENT CLAIMS are also included for the following:

(1) use of (I) in the preparation of a medicament for:

(a) the treatment of diseases related with angiogenesis;

(b) the prevention of unwanted angiogenesis;

(c) the suppression of **tumor** growth and/or regression of established **tumors**;

(d) the treatment of diseases related to inflammatory disorders, conformational disorders, type II diabetes and/or ageing;

(e) the breakdown of extracellular matrix components; and

(f) the degradation of amyloid beta and/or inhibition of amyloid beta action;

(2) treatment of a disease associated with and/or dependent on angiogenesis or amyloid deposition comprising administering (I) to a patient; and

(3) a peptide (II) of 10-150 amino acid residues, comprising the sequence 262-367 of vitronectin or its functional fragment and/or derivative.

ACTIVITY - Antiinflammatory; Antidiabetic; Cytostatic; Antiulcer; Vulnerary; Antirheumatic; Antiarthritic; Osteopathic; Antianemic; Tranquilizer; Ophthalmological; Antibacterial; Protozoacide; Nootropic; Neuroprotective.

Fibrin degradation products (FDP) were generated by **plasmin** digestion of fibrin. A model of subcutaneous **tumor** growth of a mouse C26 colon **carcinoma** was used to evaluate the effects of FDP. Male BALB/c mice were inoculated with 10 to the power of 6 C26 colon **carcinoma** cells. Mice were treated daily by subcutaneous injection with either saline or FDP for approx. 14 days. 11 days after **tumor** cell inoculation, **tumors** of the control group had reached a volume of 2719 plus or minus 366 mm3. In mice treated with FDP, the mean **tumor** growth was 719 plus or minus 188 mm3. At similar concentrations, endostatin, another molecule with the ability to stimulate tPA mediated **plasmin** formation,

suppressed **tumor** growth but was slightly less effective (**tumor** volume 1112 plus or minus 372 mm3). Treatment with tPA, which generates **plasmin**, suppressed **tumor** growth to a similar degree (**tumor** volume 492 plus or minus 215 mm3) as FDP. These results demonstrated that FDP inhibited **tumor** growth.

MECHANISM OF ACTION - Activator of **plasminogen** through tPA.

USE - (I) is useful in the preparation of a medicament for the treatment of diseases associated with and/or dependent on angiogenesis, amyloid deposition, prevention of unwanted angiogenesis, to suppress **tumor** growth and/or to regress established **tumors**, for treating diseases related to inflammatory disorders, conformational disorders, type II diabetes and/or aging, for the breakdown of extracellular matrix components, degradation of aggregated amyloid- beta and/or inhibition of amyloid- beta action. The extracellular matrix components at the site of unwanted angiogenesis are degraded upon administration of (I) (claimed). Diseases mediated by angiogenesis treated by (I) include, **cancer** and ocular neovascular disease characterized by invasion of new blood vessels into the structures of eye, such as retina or cornea. Angiogenic damage is also associated with diabetic retinopathy, retinopathy of prematurity, corneal graft rejection, neovascular glaucoma and retrolental fibroplasia and other diseases associated with neovascularization, include epidemic keratoconjunctivitis, vitamin A deficiency, contact lens overwear, atopic keratitis, chemical burns, bacterial ulcers, fungal ulcers, herpes simplex infections, protozoan infections, keratolysis, rheumatoid arthritis, systemic lupus, polyarteritis and trauma. Diseases associated with retinal/choroidal neovascularization include diabetic retinopathy, macular degeneration, sickle cell anemia, sarcoid, syphilis, pseudoxanthoma elasticum, Paget's disease, vein occlusion, diseases associated with rubeosis and diseases caused by the abnormal proliferation of fibrovascular or fibrous tissue including all forms of proliferative vitreoretinopathy. Other disorders include osteoarthritis, chronic inflammation such as ulcerative colitis, Crohn's disease and blood-born **tumors**, such as leukemias. Diseases associated with amyloid deposition include neurodegenerative diseases, e.g. kuru, Creutzfeldt-Jacob disease, conformational diseases and aging (e.g. Alzheimer's disease).

ADVANTAGE - (I) provides a very efficient method to prevent angiogenesis, as a single molecule catalyzes the formation of many **plasmin** molecules. By generating excess **plasmin**, (I) offers, in contrast to conventional strategies aimed at inhibiting proteases, a unique, efficient way to destroy the micro-environment and shrink affected pathological tissue. The method is specific for cells that express tPA, i.e. activated endothelial cells.

Dwg.0/4

L10 ANSWER 6 OF 56 WPIDS (C) 2003 THOMSON DERWENT
ACCESSION NUMBER: 2002-082332 [11] WPIDS
CROSS REFERENCE: 2001-441621 [47]; 2001-488538 [53]; 2002-065878 [09]; 2002-074630 [10]; 2002-082296 [11]; 2002-105506 [14]; 2002-470580 [50]; 2003-341108 [32]; 2003-361827 [34]; 2003-370772 [35]; 2003-370773 [35]

DOC. NO. CPI: C2002-024825
TITLE: Composition useful for delivering peptidyl drugs comprises a hydroxide releasing agent.
DERWENT CLASS: B04 D16 P32 P34
INVENTOR(S): HSU, T; LUO, E C
PATENT ASSIGNEE(S): (HSUT-I) HSU T; (LUOE-I) LUO E C; (DERM-N) DERMATRENDS INC
COUNTRY COUNT: 1
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
US 2001038862	A1	20011108	(200211)*		16
US 6558695	B2	20030506	(200338)		

APPLICATION DETAILS:

PATENT NO	KIND		APPLICATION	DATE
US 2001038862	A1	CIP of	US 1999-465098	19991216
		CIP of	US 2000-569889	20000511
		CIP of	US 2000-687937	20001013
			US 2000-737831	20001214
US 6558695	B2	CIP of	US 1999-465098	19991216
		CIP of	US 2000-569889	20000511
		CIP of	US 2000-687937	20001013
			US 2000-737831	20001214

PRIORITY APPLN. INFO: US 2000-737831 20001214; US 1999-465098 19991216; US 2000-569889 20000511; US 2000-687937 20001013

AN 2002-082332 [11] WPIDS

CR 2001-441621 [47]; 2001-488538 [53]; 2002-065878 [09]; 2002-074630 [10]; 2002-082296 [11]; 2002-105506 [14]; 2002-470580 [50]; 2003-341108 [32]; 2003-361827 [34]; 2003-370772 [35]; 2003-370773 [35]

AB US2001038862 A UPAB: 20030616
NOVELTY - A composition comprises an aqueous formulation of: a peptidyl drug (I), a hydroxide-releasing agent (II), and a carrier (III). (II) enhances the flux of (I) through the body surface.
DETAILED DESCRIPTION - An INDEPENDENT CLAIM is included for a system for topical or transdermal administration of (I) comprising: at least one reservoir containing (I) and (II); a device for maintaining the system in drug and enhancer transmitting relationship to the body surface; and a backing layer. The backing layer serves as the outer surface of the system during use.
ACTIVITY - Analgesic.
MECHANISM OF ACTION - Interferon-therapy.
USE - For the delivery of peptidyl drug through a body surface. The peptidyl drug are useful in variety of diseases e.g. pain.
ADVANTAGE - The composition is substantially free of additional permeation enhancer and organic solvents. The formulation increases the rate at which an active agent permeates the skin, and does not result in skin damage, irritation or sensitization. (II) are highly effective permeation enhancers. The formulation does not result in systemic toxicity.
Dwg.0/0

L10 ANSWER 7 OF 56 SCISEARCH COPYRIGHT 2003 THOMSON ISI
ACCESSION NUMBER: 2001:240901 SCISEARCH
THE GENUINE ARTICLE: 411AA
TITLE: A truncated **plasminogen** activator inhibitor-1 protein induces and inhibits angiostatin (kringles 1-3), a **plasminogen** cleavage product
AUTHOR: Mulligan-Kehoe M J (Reprint); Wagner R; Wieland C; Powell R
CORPORATE SOURCE: Dartmouth Med Sch, Dartmouth Coll, Dept Surg, Div Vasc Surg, Borwell 530 E, 1 Med Ctr Dr, Lebanon, NH 03756 USA (Reprint); Dartmouth Med Sch, Dartmouth Coll, Dept Surg, Div Vasc Surg, Lebanon, NH 03756 USA
COUNTRY OF AUTHOR: USA
SOURCE: JOURNAL OF BIOLOGICAL CHEMISTRY, (16 MAR 2001) Vol. 276, No. 11, pp. 8588-8596.
Publisher: AMER SOC BIOCHEMISTRY MOLECULAR BIOLOGY INC, 9650 ROCKVILLE PIKE, BETHESDA, MD 20814 USA.
ISSN: 0021-9258.
DOCUMENT TYPE: Article; Journal
LANGUAGE: English
REFERENCE COUNT: 71

ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB **Plasminogen** activator inhibitor-1 (PAI-1) is a serpin protease inhibitor that binds **plasminogen** activators (uPA and tPA) at a reactive center loop located at the carboxyl-terminal amino acid residues 320-351. The loop is stretched across the top of the active PAI-1 protein maintaining the molecule in a rigid conformation, In the latent PAI-1 conformation, the reactive center loop is inserted into one of the beta sheets, thus making the reactive center loop unavailable for interaction with the **plasminogen** activators. We truncated porcine PAI-1 at the amino and carboxyl termini to eliminate the reactive center loop, part of a **heparin** binding site, and a vitronectin binding site. The region we maintained corresponds to amino acids 80-265 of mature human PAI-1 containing binding sites for vitronectin, **heparin** (partial), up, tPA, fibrin, thrombin, and the helix F region. The interaction of "inactive" PAI-1, rPAI-1(23), with **plasminogen** and uPA induces the formation of a proteolytic protein with angiostatin properties, Increasing amounts of rPAI-1(23) inhibit the proteolytic angiostatin fragment. Endothelial cells exposed to exogenous rPAI-1(23) exhibit reduced proliferation, reduced tube formation, and 47% apoptotic cells within 48 h, Transfected endothelial cells secreting rPAI-1(23) have a 30% reduction in proliferation, vastly reduced tube formation, and a 50% reduction in cell migration in the presence of VEGF. These two studies show that rPAI-1(23) interactions with uPA and **plasminogen** can inhibit **plasmin** by two mechanisms. In one mechanism, rPAI-1(23) cleaves **plasmin** to form a proteolytic ansostatin-like protein. In a second mechanism, rPAI-1(23) can bind uPA and/or **plasminogen** to reduce the number of uPA and **plasminogen** interactions, hence reducing the amount of **plasmin** that is produced.

L10 ANSWER 8 OF 56 SCISEARCH COPYRIGHT 2003 THOMSON ISI
ACCESSION NUMBER: 2002:29645 SCISEARCH

THE GENUINE ARTICLE: 504LD
TITLE: Localization of blood coagulation factors in situ in pancreatic **carcinoma**

AUTHOR: Wojtukiewicz M Z (Reprint); Rucinska M; Zacharski L R; Kozlowski L; Zimnoch L; Piotrowski Z; Kudryk B J; Kisiel W

CORPORATE SOURCE: Med Acad Bialystok, Dept Oncol, Bialystok, Poland (Reprint); Med Acad Bialystok, Dept Pathol Anat, Bialystok, Poland; Med Acad Bialystok, Dept Surg Gastroenterol, Bialystok, Poland; Dartmouth Coll Sch Med, White River Jct, VT USA; Dept Vet Affairs Med Ctr, White River Jct, VT USA; Reg Off Ctr, White River Jct, VT USA; New York Blood Ctr, Lab Blood Coagulat Biochem, New York, NY 10021 USA; Univ New Mexico, Sch Med, Dept Pathol, Albuquerque, NM 87131 USA

COUNTRY OF AUTHOR: Poland; USA

SOURCE: THROMBOSIS AND HAEMOSTASIS, (DEC 2001) Vol. 86, No. 6, pp. 1416-1420.
Publisher: F K SCHATTAUER VERLAG GMBH, P O BOX 10 45 43, LENZHALDE 3, D-70040 STUTTGART, GERMANY.
ISSN: 0340-6245.

DOCUMENT TYPE: Article; Journal
LANGUAGE: English
REFERENCE COUNT: 44

ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB Blood coagulation is activated commonly in pancreatic **carcinoma** but the role of the **tumor** cell in this activation is undefined. Immunohistochemical procedures were applied to fixed sections of 22 cases of resected adenocarcinoma of the pancreas to determine the presence of components of coagulation and fibrinolysis pathways in situ. **Tumor** cell bodies stained for tissue factor; prothrombin; and factors VII. VIIIc. IX, X, XII, and subunit "a" of factor XIII. Fibrinogen existed throughout the **tumor** stroma. and **tumor** cells were surrounded by fibrin. Staining for tissue factor pathway inhibitor, and **plasminogen** activators was minimal and inconsistent. **Plasminogen** activator inhibitors -1, -2, and -3 were present in the **tumor** stroma, and on **tumor** cells and vascular endothelium.

Extravascular coagulation activation exists associated with pancreatic **carcinoma** cells in situ that is apparently unopposed by naturally occurring inhibitors or the **plasminogen** activator-**plasmin** system. We postulate that such local coagulation activation may regulate growth of this malignancy. These findings provide a rationale for testing agents that modulate the blood coagulation/fibrinolytic system (that inhibit **tumor** growth in other settings) in pancreatic **carcinoma**.

L10 ANSWER 9 OF 56 MEDLINE DUPLICATE 2
ACCESSION NUMBER: 2001200153 MEDLINE
DOCUMENT NUMBER: 21184081 PubMed ID: 11286474
TITLE: Differential regulation of cell proliferation and protease secretion by epidermal growth factor and amphiregulin in tumoral versus normal breast epithelial cells.

AUTHOR: Silvy M; Giusti C; Martin P M; Berthois Y

CORPORATE SOURCE: Laboratoire de Cancerologie Experimentale, EA 2671, IFR Jean Roche, Faculte de Medecine secteur Nord, Bd Pierre Dramard, 13916 Marseille Cedex 20, France.
SOURCE: BRITISH JOURNAL OF CANCER, (2001 Apr 6) 84 (7) 936-45.
Journal code: 0370635. ISSN: 0007-0920.
PUB. COUNTRY: Scotland: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200105
ENTRY DATE: Entered STN: 20010517
Last Updated on STN: 20010517
Entered Medline: 20010510

AB Amphiregulin (AR) is a **heparin**-binding epidermal growth factor (EGF)-related peptide that seems to play an important role in mammary epithelial cell growth regulation. We have investigated the regulation of AR-gene expression and -protein secretion by EGF in normal breast epithelial cells (HMECs), as well as in the tumoral breast epithelial cell lines MCF-7 and MDA-MB231. EGF induced a dose-dependent increase of AR mRNA level in both normal and tumoral cells. Thus, 10(-8)M EGF stimulated AR expression in HMECs to 140-300% of control. A similar EGF concentration increased AR mRNA level to 550% and 980% of control in MCF-7 and MDA-MB231 cells, respectively. This was accompanied by an accumulation of AR into conditioned culture media. However, HMECs secreted in response to EGF, 5-10 fold more AR than **tumour** cells. Furthermore, the potential participation of AR in the regulation of the **plasminogen** activator (PA)/**plasmin** system was investigated. Whereas HMEC-proliferation was stimulated by AR, the levels of secreted urokinase-type **plasminogen** activator (uPA) and type-1 **plasminogen** activator inhibitor (PAi-1) remained unaffected. Conversely, AR failed to regulate the proliferation of tumoral cell lines but induced an accumulation of uPA and PAi-1 into culture media. This was accompanied by an increase of the number of tumoral cells that invaded matrigel in vitro. Moreover, the presence of a neutralizing anti-uPA receptor antibody reversed the increased invasiveness of MDA-MB231 cells induced by AR. These data reveal differential behaviour of normal versus tumoral breast epithelial cells in regard to the action of AR and demonstrate that, in a number of cases, AR might play a significant role in **tumour** progression through the regulation of the PA/**plasmin** system.

L10 ANSWER 10 OF 56 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V.

ACCESSION NUMBER: 2002128248 EMBASE
TITLE: Hemostatic changes in malignancy - A review.
AUTHOR: Saxena R.; Tyagi S.
CORPORATE SOURCE: Prof. Dr. R. Saxena, Dept. of Haematology, IRCH Building, 1st Floor, All India Inst. of Medical Sciences, New Delhi 110 029, India
SOURCE: Indian Journal of Hematology and Blood Transfusion, (2001) 19/2 (39-40).
Refs: 9
ISSN: 0971-4502 CODEN: IJHTFC
COUNTRY: India
DOCUMENT TYPE: Journal; (Short Survey)

FILE SEGMENT: 025 Hematology
016 Cancer
038 Adverse Reactions Titles
037 Drug Literature Index
029 Clinical Biochemistry
LANGUAGE: English

L10 ANSWER 11 OF 56 SCISEARCH COPYRIGHT 2003 THOMSON ISI
ACCESSION NUMBER: 2000:780681 SCISEARCH
THE GENUINE ARTICLE: 362TL
TITLE: Prokaryotic expression, purification, and reconstitution of biological activities (antiprotease, **antitumor**, and **heparin**-binding) for tissue factor pathway inhibitor-2
AUTHOR: Rao C N (Reprint); Reddy P; Reeder D J; Liu Y Y; Stack S M; Kisiel W; Woodley D T
CORPORATE SOURCE: CTR PROSTATE DIS RES, 1530 E JEFFERSON ST, ROCKVILLE, MD 20852 (Reprint); NORTHWESTERN UNIV, SCH MED, DEPT DERMATOL, CHICAGO, IL 60611; NORTHWESTERN UNIV, SCH MED, DEPT OBSTET & GYNECOL, CHICAGO, IL 60611; NATL INST STAND & TECHNOL, DIV BIOTECHNOL, GAITHERSBURG, MD 20877; UNIV NEW MEXICO, SCH MED, DEPT PATHOL, SANTA FE, NM 87131
COUNTRY OF AUTHOR: USA
SOURCE: BIOCHEMICAL AND BIOPHYSICAL RESEARCH COMMUNICATIONS, (5 OCT 2000) Vol. 276, No. 3, pp. 1286-1294.
Publisher: ACADEMIC PRESS INC, 525 B ST, STE 1900, SAN DIEGO, CA 92101-4495.
ISSN: 0006-291X.
DOCUMENT TYPE: Article; Journal
FILE SEGMENT: LIFE
LANGUAGE: English
REFERENCE COUNT: 31

ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB We report the expression of tissue factor pathway inhibitor-2 (TFPI-2) (also known as PP-5, placental protein-5; MSPI, matrix-associated serine protease inhibitor) in E. coli as a 25-kDa nonglycosylated protein with a glycine substituted for aspartic acid at the amino terminus. High-level expression of TFPI-2 was obtained with pRE1 expression vector under the transcriptional and translational controls of the lambda P-L promoter and lambda c(II) ribosome-binding site, respectively, with ATG initiation codon. TFPI-2 was produced as inclusion bodies and accounted for 25-30% of the total E. coli proteins. The inclusion bodies containing TFPI-2 were solubilized with urea, sufitolyzed, purified, and refolded through a disulfide interchange reaction. The refolded E. coli TFPI-2 inhibited **plasmin** with an inhibition constant (K-i) of 5 nM that is similar with the TFPI-2 expressed in a mammalian system. The refolded E. coli TFPI-2 bound **heparin** and also inhibited **plasmin**, regardless of whether the enzyme was in the fluid phase or was bound to the membranes of HT-1080 fibrosarcoma cells. In addition, refolded E. coli TFPI-2 inhibited radiolabeled matrix degradation and Matrigel matrix invasion by HT-1080 fibrosarcoma cells and B16-F10 melanoma cells. Together, our results suggest that glycosylation is not essential for antiprotease, **antitumor**, and matrix-binding activities of TFPI-2, Based on these collective data, we conclude that a

biologically active nonglycosylated TFPI-2 can be produced in E. coli and that the protein can be produced in high-enough quantities to conduct in vivo studies for determination of the role of this inhibitor in **tumor** invasion and metastasis. (C) 2000 Academic Press.

L10 ANSWER 12 OF 56 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 2000322309 EMBASE
TITLE: Syndromes of disseminated intravascular coagulation in obstetrics, pregnancy, and gynecology: Objective criteria for diagnosis and management.
AUTHOR: Bick R.L.
CORPORATE SOURCE: Dr. R.L. Bick, 10455 North Central Expressway, Dallas, TX 75231, United States. rbick@onramp.net
SOURCE: Hematology/Oncology Clinics of North America, (2000) 14/5 (999-1044).
Refs: 247
ISSN: 0889-8588 CODEN: HCNAEQ
COUNTRY: United States
DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 010 Obstetrics and Gynecology
016 Cancer
025 Hematology
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English

AB This article presents current understanding of the causes, pathophysiology, clinical, and laboratory diagnosis, and management of fulminant and low-grade DIC, as they apply to obstetric, pregnant, and gynecologic patients. General medical complications leading to DIC, which may often be seen in these patients, are also discussed. Considerable attention has been given to interrelationships within the hemostasis system. Only by clearly understanding these pathophysiologic interrelationships can the obstetrician/gynecologist appreciate the divergent and wide spectrum of often confusing clinical and laboratory findings in patients with DIC. Objective clinical and laboratory criteria for diagnosis of DIC have been outlined to eliminate unnecessary confusion and the need to make empiric decisions regarding the diagnosis. Particularly in the obstetric patient, if a condition is observed that is associated with DIC, or if any suspicion of DIC arises from either clinical or laboratory findings, it is imperative to monitor the patient carefully with clinical and laboratory tools to assess any progression to a catastrophic event. In most instances of DIC in obstetric patients, the disease can be ameliorated easily at early stages. Many therapeutic decisions are straightforward, particularly in obstetric and gynecologic patients. For more serious and complicated cases of DIC in these patients, however, efficacy and choices of therapy will remain unclear until more information is published regarding response rates and survival patterns. Also, therapy must be highly individualized according to the nature of DIC, patient's age, origin of DIC, site and severity of hemorrhage or thrombosis, and hemodynamic and other clinical parameters. Finally, many syndromes that are often categorized as organ-specific disorders and are sometimes identified as independent disease entities, such as AFE syndrome, HELLP syndrome, adult shock lung syndrome, eclampsia, and many others, either share common pathophysiology with DIC or are simply a form of DIC. These entities

represent the varied modes of clinical expression of DIC and illustrate the diverse clinical and anatomic manifestations of this syndrome.

L10 ANSWER 13 OF 56 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 2000417235 EMBASE
TITLE: Disseminated intravascular coagulation and purpura fulminans secondary to infection.
AUTHOR: Faust S.N.; Heyderman R.S.; Levin M.
CORPORATE SOURCE: S.N. Faust, Department of Paediatrics, Imperial Coll. School of Medicine, Norfolk Place, London W2 1PG, United Kingdom
SOURCE: Bailliere's Best Practice and Research in Clinical Haematology, (2000) 13/2 (179-197).
Refs: 142
ISSN: 1521-6926 CODEN: BBPHFJ
COUNTRY: United Kingdom
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 004 Microbiology
005 General Pathology and Pathological Anatomy
025 Hematology
037 Drug Literature Index
038 Adverse Reactions Titles
LANGUAGE: English
SUMMARY LANGUAGE: English
AB Infection is one of the commonest causes of disseminated intravascular coagulation (DIC). DIC is a complex disorder that results from an imbalance of the pro- and anticoagulant regulatory pathways. This chapter will explain the cellular and molecular basis of the disorder and consider the rationale behind current and experimental treatment strategies.

L10 ANSWER 14 OF 56 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 2000180340 EMBASE
TITLE: Disseminated intravascular coagulopathy (DIC): Pathophysiology, laboratory diagnosis, and management.
AUTHOR: Senno S.L.; Pechet L.; Bick R.L.
CORPORATE SOURCE: Dr. L. Pechet, 365 Plantation Street, Worcester, MA 01605, United States
SOURCE: Journal of Intensive Care Medicine, (2000) 15/3 (144-158).
Refs: 62
ISSN: 0885-0666 CODEN: JICME3
COUNTRY: United States
DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 005 General Pathology and Pathological Anatomy
025 Hematology
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English
AB Disease entities such as sepsis, shock, obstetric complications, and **neoplasms** share the process of disseminated intravascular coagulopathy (DIC) as a secondary complication. Regardless of the initiating event, DIC results from the activation of the virtually unregulated coagulation cascade, characterized by the generation of thrombin with fibrin deposition within the micro- and macrovascular systems (i.e., multiple thrombi), combined with a hemorrhagic

diathesis. The counteraction by the fibrinolytic cascade is variable and is characterized by the conversion of **plasminogen** to **plasmin**, the latter functioning as a potent proteolytic enzyme, capable of degrading fibrinogen, fibrin, and several clotting factors. The kinin and complement cascades also partake in the promotion of DIC. In addition, antithrombin (AT), proteins C and S, antiplasmin, and **plasminogen** activator inhibitor 1, play a functional role in curtailing the activation of the coagulation and fibrinolytic mechanisms, but they too may be affected by the DIC process, particularly because a marked decrease in AT takes place in severe cases. The laboratory findings of DIC are as variable as the underlying clinical presentation and usually include elevation of D-dimer (a product of lysed fibrin), fibrinogen degradation products (FDP), as well as prolongation of prothrombin time (PT), partial thromboplastin time (PTT), and thrombin time, accompanied by thrombocytopenia and hypofibrinogenemia (noted mostly in obstetrical cases). Because some of these assays are not specific for the diagnosis of DIC, we propose the use of a new, simple, and cost effective panel: D-dimer, FDP, and AT. Elevations in FDP and D-dimer are sensitive for the diagnosis of DIC and a marked drop in AT establishes a poor prognosis. Aside from the treatment of the underlying triggering event, a consensus with regard to the most effective management of DIC has not been established. Herein we summarize the rationale for the use of conventional therapeutic modalities such as fresh frozen plasma, cryoprecipitate, platelet and clotting factor concentrates, as well as the use of new alternatives. The use of AT infusions to maintain plasma levels of 150% of normal shows great promise in severe cases. A fundamental understanding of the pathophysiology of DIC combined with an appreciation for efficient laboratory testing will allow for the most comprehensive diagnostic and therapeutic alternatives.

L10 ANSWER 15 OF 56 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 2000011798 EMBASE
TITLE: [Coagulation disorders as emergency in **cancer** patients].
GERINNUNGSSTORUNGEN ALS NOTFALL BEI ONKOLOGISCHEN PATIENTEN.
AUTHOR: Kemkes-Matthes B.; Fenchel K.; Matzdorff A.
CORPORATE SOURCE: Dr. B. Kemkes-Matthes, Zentrum Innere Medizin, Justus Liebig Universitat Giessen, Medizinische Klinik IV, Klinikstrasse 36, D-35385 Giessen, Germany. Bettina.Kemkes-Matthes@innere.med.uni-giessen.de
SOURCE: Onkologe, (1999) 5/12 (1083-1089).
Refs: 24
ISSN: 0947-8965 CODEN: ONKOF4
COUNTRY: Germany
DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 016 Cancer
025 Hematology
037 Drug Literature Index
038 Adverse Reactions Titles
LANGUAGE: German

L10 ANSWER 16 OF 56 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 1999165928 EMBASE
TITLE: Vitronectin.
AUTHOR: Schvartz I.; Seger D.; Shaltiel S.

CORPORATE SOURCE: S. Shaltiel, Department of Biological Regulation, The Weizmann Institute of Science, IL-76100 Rehovot, Israel. lishalt@wiccmail.weizmann.ac.il

SOURCE: International Journal of Biochemistry and Cell Biology, (1999) 31/5 (539-544).
Refs: 15
ISSN: 1357-2725 CODEN: IJBBFU
PUBLISHER IDENT.: S 1357-2725(99)00005-9
COUNTRY: United Kingdom
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 002 Physiology
029 Clinical Biochemistry
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English

AB Vitronectin is a multifunctional glycoprotein present in blood and in the extracellular matrix. It binds glycosaminoglycans, collagen, **plasminogen** and the urokinase-receptor, and also stabilizes the inhibitory conformation of **plasminogen** activation inhibitor-1. By its localization in the extracellular matrix and its binding to **plasminogen** activation inhibitor-1, vitronectin can potentially regulate the proteolytic degradation of this matrix. In addition, vitronectin binds to complement, to **heparin** and to thrombin-antithrombin III complexes, implicating its participation in the immune response and in the regulation of clot formation. The biological functions of vitronectin can be modulated by proteolytic enzymes, and by exo- and ecto-protein kinases present in blood. Vitronectin contains an RGD sequence, through which it binds to the integrin receptor .alpha.(v).beta.3, and is involved in the cell attachment, spreading and migration. Antibodies against .alpha.(v).beta.3 or synthetic peptides containing an RGD sequence are now being tested as therapeutic agents in the treatment of human **cancers**, bone diseases (e.g. osteoporosis) and in pathological disorders which involve angiogenesis. Copyright (C) 1999 Elsevier Science Ltd.

L10 ANSWER 17 OF 56 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 2000004885 EMBASE
TITLE: Multi-drug strategies are necessary to inhibit the synergistic mechanism causing tissue damage and organ failure in post infectious sequelae.
AUTHOR: Ginsburg I.
CORPORATE SOURCE: I. Ginsburg, Department of Oral Biology, Hebrew University, Hadassah Faculty of Dental Medicine, Jerusalem, Israel. ginsburg@cc.huji.ac.il
SOURCE: Inflammopharmacology, (1999) 7/3 (207-217).
Refs: 56
ISSN: 0925-4692 CODEN: IAOAES
COUNTRY: Netherlands
DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 004 Microbiology
026 Immunology, Serology and Transplantation
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English
AB The paper discusses the principal evidence that supports the concept that cell and tissue injury in infectious and post-infectious and inflammatory sequelae might involve a deleterious synergistic

interaction among microbial- and host-derived pro-inflammatory agonists. Experimental models had proposed that a rapid cell and tissue injury might be induced by combinations among subtoxic amounts of three major groups of agonists generated both by microorganisms and by the host's own defense systems. These include: (1) oxidants: superoxide, H2O2, OH', oxidants generated by xanthine-xanthine-oxidase, ROO', HOCl, NO, OONO'-, (2) the membrane-injuring and perforating agents, microbial hemolysins, phospholipases A2 and C, lysophosphatides, bactericidal cationic proteins, fatty acids, bile salts and the attack complex of complement a, certain xenobics and (3) the highly cationic proteinases, elastase and cathepsin G, as well as collagenase, **plasmin**, trypsin and a variety of microbial proteinases. Cell killing by combinations among the various agonists also results in the release of membrane-associated arachidonate and metabolites. Cell damage might be further enhanced by certain cytokines either acting directly on targets or through their capacity to prime phagocytes to generate excessive amounts of oxidants. The microbial cell wall components, lipoteichoic acid (LTA), lipopolysaccharides (LPS) and peptidoglycan (PPG), released following bacteriolysis, induced either by cationic proteins from neutrophils and eosinophils or by beta lactam antibiotics, are potent activators of macrophages which can release oxidants, cytolytic cytokines and NO. The microbial cell wall components can also activate the cascades of coagulation, complement and fibrinolysis. All these cascades might further synergize with microbial toxins and metabolites and with phagocyte-derived agonists to amplify tissue damage and to induce septic shock, multiple organ failure, 'flesh-eating' syndromes, etc. The long persistence of non-biodegradable bacterial cell wall components within activated macrophages in granulomatous inflammation might be the result of the inactivation by oxidants and proteinases of bacterial autolytic wall enzymes (muramidases). The unsuccessful attempts in recent clinical trials to prevent septic shock by the administration of single antagonists is disconcerting. It does suggest however that, since tissue damage in post-infectious syndromes is most probably the end result of synergistic interactions among a multiplicity of agents, only agents which might depress bacteriolysis in vivo and 'cocktails' of appropriate antagonists, but not single antagonists, if administered at the early phases of infection especially to patients at high risk, might help to control the development of post-infectious syndromes. However, the use of adequate predictive markers for sepsis and other post-infectious complications is highly desirable. Although it is conceivable that anti- inflammatory strategies might also be counter-productive as they might act as 'double-edge swords', intensive investigations to devise combination therapies are warranted. The present review also lists the major anti-inflammatory agents and strategies and combinations among them which have been proposed in the last few years for clinical treatments of sepsis and other post-infectious complications.

L10 ANSWER 18 OF 56 MEDLINE DUPLICATE 3
ACCESSION NUMBER: 1999332328 MEDLINE
DOCUMENT NUMBER: 99332328 PubMed ID: 10402490
TITLE: Modulation of biological phenotypes for **tumor** growth and metastasis by target-specific biological inhibitors in gastric **cancer**.
AUTHOR: Rha S Y; Noh S H; Kim T S; Yoo N C; Roh J K; Min J S;

Kim B S
CORPORATE SOURCE: Yonsei Cancer Research Institute, Yonsei University College of Medicine, Seoul, Korea.
SOURCE: INTERNATIONAL JOURNAL OF MOLECULAR MEDICINE, (1999 Aug) 4 (2) 203-12.
Journal code: 9810955. ISSN: 1107-3756.
PUB. COUNTRY: Greece
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199909
ENTRY DATE: Entered STN: 19990913
Last Updated on STN: 20000303
Entered Medline: 19990901

AB For **tumor** progression, a cascade of linked sequential biological events is essential. We tried to test whether biological therapy can modulate specific biological phenotypes and increase the anti-**tumor** effect when combined with chemotherapy. Five human gastric **cancer** cell lines (YCC-1, YCC-2, YCC-3, YCC-7, AGS) were used in these studies. Pentosan polysulfate (PPS) as a **heparin**-binding growth factor inhibitor, **Tranexamic** acid as a **plasmin** inhibitor, Lovastatin as an adhesion inhibitor and Adriamycin as a chemotherapeutic agent were selected. The effects of each drug on colony formation and **tumor** cell proliferation were evaluated by soft agar assay and cell proliferation assay, respectively to test direct anti-**tumor** effect. The expression of uPA, PAI-1 was determined by ELISA, while MMPs activity was evaluated by zymography. PPS suppressed the colony-forming activity as much as Adriamycin did, but it showed only cytostatic effects in cell proliferation assay. Migration capacity using Boyden chamber assay was more closely correlated with adhesive capacity than uPA or MMP-2 expression. The motility inhibitory effect of **Tranexamic** acid was observed in the YCC-7 cell line, which expressed all the required biological phenotypes for migration. In AGS, with high cell motility and adhesiveness, the adhesion was inhibited by Lovastatin and most of the inhibitory effect was recovered by Mevalonate. When PPS was combined with Adriamycin on the Adriamycin-resistant, midkine (MK) gene expressing YCC-7 cell line, the growth inhibition rate increased up to 84%, while that for a single treatment of PPS or Adriamycin was 40% and 22%, respectively (p=0.001). When we combined **Tranexamic** acid and Adriamycin, we observed the synergistic effect in YCC-3 and YCC-7, while no combined effect was found in YCC-1. The combination of Lovastatin and Adriamycin did not show any combined effects in any of the cell lines. In conclusion, a synergistic anti-proliferative effect (chemo-sensitization) with combined chemo-biotherapy was found in **cancer** cells with specific biological target, MK. The anti-motility effect was the greatest when the gastric **cancer** cells expressed all the specific biological phenotypes.

L10 ANSWER 19 OF 56 SCISEARCH COPYRIGHT 2003 THOMSON ISI
ACCESSION NUMBER: 2000:87446 SCISEARCH
THE GENUINE ARTICLE: 277VR
TITLE: Disseminated intravascular coagulation - Clinical and pathophysiological mechanisms and manifestations
AUTHOR: Bick R L (Reprint); Arun B; Frenkel E P

CORPORATE SOURCE: 10455 N CENT EXPRESSWAY, SUITE 109, DALLAS, TX 75231 (Reprint); UNIV TEXAS, SW MED CTR, DEPT MED, DIV HEMATOL ONCOL, DALLAS, TX
COUNTRY OF AUTHOR: USA
SOURCE: HAEMOSTASIS, (25 JAN 1999) Vol. 29, No. 2-3, pp. 111-134.
Publisher: KARGER, ALLSCHWILERSTRASSE 10, CH-4009 BASEL, SWITZERLAND.
ISSN: 0301-0147.
DOCUMENT TYPE: Article; Journal
FILE SEGMENT: LIFE
LANGUAGE: English
REFERENCE COUNT: 178

ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB Disseminated intravascular coagulation (DIC) is a complex disorder, with pathophysiology being variable and highly dependent upon the triggering event(s), host response(s) and comorbid conditions. As a result of these complicated interactions, the clinical expression and laboratory findings are varied, thereby affecting the specifics of diagnosis and therapeutic approaches. The highly complex and variable pathophysiology of DIC often results in a lack of uniformity in clinical manifestations, a lack of consensus in the specific appropriate laboratory criteria of diagnosis, and a lack of specific therapeutic modalities. Indeed, recommendations for therapy are often difficult because the morbidity and survival is more dependent on the specific cause of DIC and because the generally used specific therapeutic approaches, which include for example **heparin**, low-molecular-weight-**heparin** antithrombin concentrate and protein C concentrate, have never been subjected to objective prospective randomized trials, except antithrombin concentrates. An analysis of the complex a nd varied pathophysiological events in DIC provide objective guidelines and criteria for the clinical diagnosis, the laboratory diagnosis, and the definition of severity. These data compounded by an understanding of complex and varied pathophysiology can be used for objective evaluation of therapeutic responses and results. DIC is an intermediary mechanism of disease usually seen in association with well-defined clinical disorders. The pathophysiology of DIC serves as an intermediary mechanism in many disease processes, which sometimes remain organ specific. This catastrophic syndrome spans all areas of medicine and presents a broad clinical spectrum that is confusing to many. Most physicians consider DIC to be a systemic hemorrhagic syndrome; however, this is only because hemorrhage is evident and often impressive. Less commonly appreciated is the profound microvascular thrombosis and sometimes, large vessel thrombosis. The hemorrhage is often simple to contend with in patients with fulminant DIG, but it is the small- and large-vessel thrombosis, with impairment in blood flow, ischemia, and associated end-organ damage that usually leads to irreversible morbidity and mortality. In conclusion, the pathophysiological mechanisms, clinical, and laboratory manifestations of DIC are complex in part due to interrelationships within the hemostasis system. Only by clearly understanding these extraordinarily complex pathophysiological interrelationships can the clinician and laboratory scientist appreciate the divergent and wide spectrum of often confusing clinical and laboratory findings in patients with DIG. Many therapeutic decisions to be made are controversial and lack validation. Nevertheless, newer antithrombotic agents, and

agents which can block, blunt or modify cytokine activity and the activity of vasoactive substances appear to be of value. The complexity and variable degree of clinical expression suggests that therapy should be individualized depending on the nature of DIG, age, etiology of DIG, site and severity of hemorrhage or thrombosis and hemodynamics and other appropriate clinical parameters.

L10 ANSWER 20 OF 56 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
DUPLICATE 4

ACCESSION NUMBER: 1999:253665 BIOSIS
DOCUMENT NUMBER: PREV199900253665
TITLE: Hyperfibrinolysis in a case of myelodysplastic syndrome with leukemic spread of mast cells.
AUTHOR(S): Wimazal, F.; Sperr, W. R.; Horny, H.-P.; Carroll, V.; Binder, B. R.; Fonatsch, C.; Walchshofer, S.; Foedinger, M.; Schwarzinger, I.; Samorapoompichit, P.; Chott, A.; Dvorak, A. M.; Lechner, K.; Valent, P. (1)
CORPORATE SOURCE: (1) Dept. of Internal Medicine I, Division of Hematology and Hemostaseology, Waehringer Guertel 18-20, A-1090, Vienna Austria
SOURCE: American Journal of Hematology, (May, 1999) Vol. 61, No. 1, pp. 66-77.
ISSN: 0361-8609.
DOCUMENT TYPE: Article
LANGUAGE: English
SUMMARY LANGUAGE: English

AB Mast cells (MC) are multipotent hemopoietic effector cells producing diverse mediators like histamine, **heparin**, or tissue type **plasminogen** activator. We report a 75-year-old male patient with myelodysplastic syndrome (MDS) of recent onset (3 months' history) associated with a massive leukemic spread of immature tryptase+ MC (tentative term: myelomastocytic leukemia). The patient presented with pancytopenia, bleeding, hypofibrinogenemia, and an increased cellular tryptase level. Moreover, an excessive elevation of **plasmin**-antiplasmin complexes (9,200 ng/ml; normal range: 10-150), an elevated D-dimer, and an increase in thrombin-antithrombin III complexes were found. The identity of the circulating MC was confirmed by immunophenotyping (CD117/c-kit+, CD123/IL-3Ralpha-, CD11b/C3biR-), biochemical analysis (cellular ratio (ng:ng) of tryptase to histamine >1), and electron microscopy. Bone marrow (bm) examination showed trilineage dysplasia (17% blasts), 30% diffusely scattered MC, and a complex karyotype. No dense, compact MC infiltrates (mastocytosis) were detectable in bm sections. Despite hyperfibrinolysis and mediator syndrome (flushing, headache), the patient received remission induction polychemotherapy (DAV) followed by two cycles of consolidation with intermediate dose ARA-C (12 X 1 g/m2/day on days 1, 3, and 5). He entered complete remission after the first chemotherapy cycle without evidence of recurring MDS. Moreover, in response to chemotherapy, the hyperfibrinolysis and mediator syndrome resolved, and the circulating c-kit+ MC disappeared. We suggest consideration of polychemotherapy as a therapeutic option in patients with high-risk MDS of recent onset, even in the case of MC lineage involvement.

L10 ANSWER 21 OF 56 SCISEARCH COPYRIGHT 2003 THOMSON ISI
ACCESSION NUMBER: 1999:648426 SCISEARCH

THE GENUINE ARTICLE: 227RR
TITLE: Anticoagulation and anticoagulation reversal with cardiac surgery involving cardiopulmonary bypass: An update
AUTHOR: Despotis G J (Reprint); Joist J H
CORPORATE SOURCE: WASHINGTON UNIV, SCH MED, DEPT ANESTHESIOL, BOX 660, ST LOUIS, MO 63110 (Reprint); WASHINGTON UNIV, SCH MED, DEPT PATHOL, ST LOUIS, MO 63110; ST LOUIS UNIV, SCH MED, DEPT PATHOL, ST LOUIS, MO 63104; ST LOUIS UNIV, SCH MED, DEPT INTERNAL MED, ST LOUIS, MO 63104
COUNTRY OF AUTHOR: USA
SOURCE: JOURNAL OF CARDIOTHORACIC AND VASCULAR ANESTHESIA, (AUG 1999) Vol. 13, No. 4, Supp. [1], pp. 18-29. Publisher: W B SAUNDERS CO, INDEPENDENCE SQUARE WEST CURTIS CENTER, STE 300, PHILADELPHIA, PA 19106-3399. ISSN: 1053-0770.
DOCUMENT TYPE: Article; Journal
FILE SEGMENT: CLIN
LANGUAGE: English
REFERENCE COUNT: 117

ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB Accelerated thrombin generation is central to the development of hemostatic abnormalities during cardiopulmonary bypass (CPB) that are associated with both thromboembolic complications and serious, abnormal breeding. Thrombin not only converts fibrinogen to fibrin, but also activates platelets and coagulation factors V, VIII, and XI and causes release of von Willebrand factor from vascular endothelium. Thrombin can also downregulate the hemostatic system by inducing formation of platelet inhibitory agents, such as nitric oxide and prostacyclin, and release of tissue **plasminogen** activator, facilitating activation of protein C, and releasing tissue factor pathway inhibitor. Excessive thrombin activity may also result in substantial consumption of platelets, fibrinogen, and labile coagulation factors and abnormal bleeding. Elevated tissue **plasminogen** activator levels secondary to activation of the contact system and surgery catalyze the formation of **plasmin**, which also consumes or internalizes platelet glycoprotein receptors and coagulation factors V,VIII, and fibrinogen. **Heparin** can reduce the generation of and mediate neutralization of excessive and CPB-associated thrombin activity. **Heparin** anticoagulation is commonly monitored with the activated clotting time (ACT). However, the ACT may be prolonged by factors other than **heparin** during CPB, such as hemodilution and hypothermia, and therefore may not accurately reflect the extent of anticoagulation by **heparin**. Aprotinin, a nonspecific serine protease inhibitor used with CPB, can also prolong celite-based ACT values, rendering it less reliable for monitoring **heparin** anticoagulation. Therefore, several alternative anticoagulation strategies have been recommended when aprotinin is used, such as a higher celite ACT trigger (>750 seconds), monitoring of whole brood **heparin** concentrations (eg, >2.7 U/mL), or administration of **heparin** based on a CPB duration-dependent, fixed-dose regimen. Administration of **heparin** doses higher than those generally recommended, as guided by predetermined, patient-specific whole blood **heparin** concentration measurements during bypass, can reduce excessive thrombin-mediated consumption of platelets and coagulation factors as well as post-CPB blood loss and blood component

transfusions. New modalities of improving suppression of excess thrombin generation during CPB include use of **heparin** -bonded CPB circuits, **heparin** cofactor If or related analogs, supplemental antithrombin ill, direct thrombin inhibitors (eg, hirudin, argatroban), and inhibitors of the contact and tissue factor pathways. The safety and efficacy of these approaches remains to be established by additional, appropriately powered, prospective studies. Copyright (C) 1999 by W.B. Saunders Company.

L10 ANSWER 22 OF 56 JAPIO COPYRIGHT 2003 JPO
ACCESSION NUMBER: 1998-114796 JAPIO
TITLE: PLASMID FRAGMENT HAVING INHIBITORY EFFECT ON **TUMOR** METASTASIS PROLIFERATION AND PREPARATION OF THE SAME
INVENTOR: MORIKAWA WATARU; MIYAMOTO SEIJI
PATENT ASSIGNEE(S): CHEMO SERO THERAPEUT RES INST
PATENT INFORMATION:

PATENT NO	KIND	DATE	ERA	MAIN IPC
JP 10114796	A	19980506	Heisei	C07K014-745

APPLICATION INFORMATION
STN FORMAT: JP 1996-287651 19961009
ORIGINAL: JP08287651 Heisei
PRIORITY APPLN. INFO.: JP 1996-287651 19961009
SOURCE: PATENT ABSTRACTS OF JAPAN (CD-ROM), Unexamined Applications, Vol. 1998

AN 1998-114796 JAPIO
AB PROBLEM TO BE SOLVED: To obtain the subject new protein fragment useful for clinical treat ment for solid **cancers** such as lung **cancer** and colon **cancer**, showing **heparin**- binding properties, comprising an elastase decomposition product of lys- **plasminogen**.
SOLUTION: This new **plasminogen** fragment comprises an elastase decomposition product of lys-**plasminogen** and has inhibitory effects on **tumor** metastasis proliferation and **heparin** binding properties and is useful for clinical treatment for solid **cancers** represented by lung **cancer** and colon **cancer**. The **plasminogen** is obtained by directly adding **plasmin** to a **plasminogen**-containing solution or indirectly and naturally digesting the **plasminogen** by using **tranexamic** acid, etc., to prepare lys-**plasminogen**, then treating the lys **plasminogen** with elastase, passing the decomposition product-containing solution through a carrier using **heparin** as a ligand and adsorbing and eluting.
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L10 ANSWER 23 OF 56 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER: 1999:20949 BIOSIS
DOCUMENT NUMBER: PREV199900020949
TITLE: POEMS syndrome with vascular lesions: A role for interleukin-1 beta and interleukin-6 increase. A case report.
AUTHOR(S): Bova, Giovanni (1); Pasqui, Anna Laura; Saletti, Marco; Bruni, Fulvio; Auteri, Alberto
CORPORATE SOURCE: (1) U.O. Immunologia Clinica, Policlinico Le Scotte,

53100 Siena Italy
SOURCE: Angiology, (Nov., 1998) Vol. 49, No. 11, pp. 937-940. ISSN: 0003-3197.
DOCUMENT TYPE: Article
LANGUAGE: English
AB The authors describe the case of a 60-year-old man with POEMS syndrome associated with vascular lesions. The patient had osteosclerotic myeloma IgA (lambda), polyneuropathy, endocrinopathy, and skin changes. Subsequently, he developed gangrene of the lower limbs with no response to **heparin** therapy. The humoral study showed thrombocythemia, high levels of interleukin-1beta (IL-1beta) and IL-6 and of some coagulative/fibrinolytic and endothelial factors (von Willebrand factor, **plasmin**-antiplasmin complexes, **plasminogen** activator, and endothelial adhesion molecule ICAM-1). The authors suggest that these factors, induced by the increased levels of cytokines, could be responsible for microvascular damage, gangrene, and **heparin** resistance.

L10 ANSWER 24 OF 56 MEDLINE DUPLICATE 5
ACCESSION NUMBER: 1998189141 MEDLINE
DOCUMENT NUMBER: 98189141 PubMed ID: 9521847
TITLE: Sulfated glycosaminoglycans enhance **tumor** cell invasion in vitro by stimulating **plasminogen** activation.
AUTHOR: Brunner G; Reimbold K; Meissauer A; Schirrmacher V; Erkell L J
CORPORATE SOURCE: Division of Cellular Immunology, German Cancer Research Centre, Heidelberg, Germany.. Georg.Brunner@man.ac.uk
SOURCE: EXPERIMENTAL CELL RESEARCH, (1998 Mar 15) 239 (2) 301-10.
Journal code: 0373226. ISSN: 0014-4827.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199804
ENTRY DATE: Entered STN: 19980422
Last Updated on STN: 20000303
Entered Medline: 19980416
AB Metastasizing **tumor** cells invade host tissues by degrading extracellular matrix constituents. We report here that the highly sulfated glycosaminoglycans, **heparin** and heparan sulfate, as well as the sulfated polysaccharide, fucoidan, significantly enhanced **tumor** cell invasion in vitro into fibrin, the basement membrane extract, Matrigel, or through a basement membrane-like extracellular matrix. The enhancement of **tumor** cell invasion was due to a stimulation of the proteolytic cascade of **plasminogen** activation since the effect required **plasminogen** activation and was abolished by inhibitors of urokinase-type **plasminogen** activator (uPA) or **plasmin**. Sulfated polysaccharides enhanced five reactions of **tumor**-cell initiated **plasminogen** activation in a dose-dependent manner. They amplified **plasminogen** activation in culture supernatants up to 70-fold by stimulating (i) pro-uPA activation by **plasmin** and (ii) **plasminogen** activation by uPA. (iii) In addition, sulfated

polysaccharides partially protected **plasmin** from inactivation by alpha 2-antiplasmin. Sulfated polysaccharides also stimulated **tumor**-cell associated **plasminogen** activation, e.g., (iv) cell surface pro-uPA activation by **plasmin** and (v) **plasminogen** activation by cell surface uPA. These results suggest that sulfated glycosaminoglycans liberated by **tumor**-cell mediated extracellular matrix degradation in vivo might amplify pericellular **plasminogen** activation and locally enhance **tumor** cell invasion in a positive feedback manner.

L10 ANSWER 25 OF 56 MEDLINE DUPLICATE 6
ACCESSION NUMBER: 1998312583 MEDLINE
DOCUMENT NUMBER: 98312583 PubMed ID: 9650563
TITLE: SP220K is a novel matrix serine proteinase.
AUTHOR: Thaon S; Auberger P; Rossi B; Poustis-Delpont C
CORPORATE SOURCE: Laboratoire de Biochimie, Faculte de Medecine, Nice, France.
SOURCE: INTERNATIONAL JOURNAL OF CANCER, (1998 Jul 17) 77 (2) 264-70.
Journal code: 0042124. ISSN: 0020-7136.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199807
ENTRY DATE: Entered STN: 19980731
Last Updated on STN: 20000824
Entered Medline: 19980717

AB Matrix proteinases play a critical role in extracellular matrix remodeling, which is particularly involved in **cancer** invasion and metastasis. We have previously characterized and purified a new tetrameric serine proteinase (SP220K) from human kidney clear cell **carcinoma** plasma membranes. Here, we report that SP220K exhibits gelatinase activity as assessed both in solution and by zymography. Optimum gelatinase activity ranges between pH 7.5 to pH 9.0. Fibronectin and type I collagen were hydrolyzed by SP220K, at variance with laminin and type IV collagen. Like other trypsin-like fibronectin degrading proteinases, SP220K released the 29-kDa N-terminal **heparin**-binding domain of fibronectin. By using a panel of proteinase inhibitors, we found that the inhibition profile of SP220K was different from that of other known serine proteinases such as thrombin, trypsin, **plasmin, plasminogen** activators and tryptase. Altogether, our results indicate that SP220K corresponds to a novel matrix proteinase that exhibits a marked specificity for fibronectin and type I collagen.

L10 ANSWER 26 OF 56 JICST-EPlus COPYRIGHT 2003 JST
ACCESSION NUMBER: 980286776 JICST-EPlus
TITLE: Fundamental study of full-automatic coagulation fibrinolysis measuring device BCS, and usefulness and problems in routine test.
AUTHOR: OKUFUJI YUKIKO; MIZUTANI KUMI; FUKUDA TERUKO; SHIMAZU CHISATO; NISHIDA JUNJI; MIYAZAWA YUKIHISA
CORPORATE SOURCE: Teikyo Univ., Hosp.
SOURCE: Rinsho Kensa Kiki, Shiyaku (Journal of Clinical Laboratory Instruments and Reagents), (1998) vol. 21,

no. 1, pp. 37-47. Journal Code: Y0874A (Fig. 7, Tbl. 3, Ref. 9)
ISSN: 0386-5215
PUB. COUNTRY: Japan
DOCUMENT TYPE: Journal; Article
LANGUAGE: Japanese
STATUS: New

AB This paper describes the above bearing coagulation system (BCS) that can simultaneously measure various coagulation and fibrinolytic tests by 3 measuring methods (coagulation time, synthetized substrate, and immunoassay methods) and its measurement principle (centrifugation-type colorimetric method). This paper then evaluates the performance of BCS.In the evaluation of the above instrument, simultaneous reproducibility (samples from patients at 3 different concentrations), daily precision (control for coagulation test), effect of coexistent materials (Hb, bilirubin - free type/conjugated type, and chyle) and **heparin** concentration, dilution linearity, and correlation with current methods (coagulation time, synthetic substrate, and immunoassay methods) were examined for the following 10 items : prothrombin time, activated partial thromboplastin time, fibrinogen, thrombotest, hepaplastin test, anti-thrombin T3, **plasminogen** , .ALPHA.2 **plasmin** inhibitor, protein C, and fibrin degradation products.The 12 cases with multiple myeloma showing different results for fibrinogen were re-examined.

L10 ANSWER 27 OF 56 SCISEARCH COPYRIGHT 2003 THOMSON ISI
ACCESSION NUMBER: 1998:47597 SCISEARCH
THE GENUINE ARTICLE: YP120
TITLE: What have mast cells to do with edema formation, the consecutive repair and fibrinolysis?
AUTHOR: Valent P (Reprint); Sillaber C; Baghestanian M; Bankl H C; Kiener H P; Lechner K; Binder B R
CORPORATE SOURCE: UNIV VIENNA, DEPT INTERNAL MED 1, DIV HEMATOL & & HEMOSTASEOL, WAHRINGER GURTEL 18-20, A-1090 VIENNA, AUSTRIA (Reprint); UNIV VIENNA, INST PHYSIOL, A-1090 VIENNA, AUSTRIA; UNIV VIENNA, INST CLIN PATHOL, A-1090 VIENNA, AUSTRIA; UNIV VIENNA, DEPT INTERNAL MED 3, DIV RHEUMATOL, A-1090 VIENNA, AUSTRIA
COUNTRY OF AUTHOR: AUSTRIA
SOURCE: INTERNATIONAL ARCHIVES OF ALLERGY AND IMMUNOLOGY, (JAN 1998) Vol. 115, No. 1, pp. 2-8.
Publisher: KARGER, ALLSCHWILERSTRASSE 10, CH-4009 BASEL, SWITZERLAND.
ISSN: 1018-2438.
DOCUMENT TYPE: General Review; Journal
FILE SEGMENT: LIFE
LANGUAGE: English
REFERENCE COUNT: 50

ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB Mast cells (MC) have been implicated in the activation of vascular endothelial cells, capillary leak formation, transmigration of white blood cells, and translocation of fibrinogen (and other plasma molecules) into the tissues, with consecutive edema formation. However, the mechanisms of repair that lead to tissue reconstitution after MC activation and edema formation have not been defined so far. In the present article, the possible contribution of MC to repair, in particular fibrinolysis, is discussed. Thus,

accumulating evidence exists that human MC express and release the tissue-type **plasminogen** activator (tPA) in a constitutive manner. MC also express the urokinase receptor (uPAR) and **heparin**. Most importantly, however, MC lack **plasminogen** activator inhibitors (PAI-1, PAI-2, PAI-3). In line with this 'pro-fibrinolytic' profile of antigens, MC supernatants induce **plasminogen**-to-**plasmin** conversion and fibrin clot lysis in vitro. The c-kit ligand SCF upregulates uPAR expression, and the release of tPA from MC. These observations point to an important role of MC in endogenous fibrinolysis, a hitherto unrecognized (repair) function of this cell.

L10 ANSWER 28 OF 56 MEDLINE DUPLICATE 7
ACCESSION NUMBER: 1998058698 MEDLINE
DOCUMENT NUMBER: 98058698 PubMed ID: 9398056
TITLE: Retinoic acid-enhanced invasion through reconstituted basement membrane by human SK-N-SH neuroblastoma cells involves membrane-associated tissue-type **plasminogen** activator.
AUTHOR: Tiberio A; Farina A R; Tacconelli A; Cappabianca L; Gulino A; Mackay A R
CORPORATE SOURCE: Department of Experimental Medicine, University of L'Aquila, Italy.
SOURCE: INTERNATIONAL JOURNAL OF CANCER, (1997 Nov 27) 73 (5) 740-8.
Journal code: 0042124. ISSN: 0020-7136.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199712
ENTRY DATE: Entered STN: 19980116
Last Updated on STN: 20000303
Entered Medline: 19971224

AB Al-trans retinoic acid (RA) enhanced human, S-type, SK-N-SH neuroblastoma cell invasion of reconstituted basement membrane in vitro but did not induce terminal differentiation of this cell line. In contrast to basal invasion, which was urokinase (uPA)- and **plasmin**-dependent, RA-enhanced invasion was dependent on tissue-type **plasminogen** activator (t-PA) and **plasmin** activity. Neither basal nor RA-enhanced invasion involved TIMP-2 inhibitable metalloproteinases. Enhanced invasion was associated with the induction of t-PA expression, increased expression of the putative t-PA receptor amphoterin, increased association of t-PA with cell membranes and increased net membrane-associated PA activity. Enhanced invasion was not associated with significant changes in the expression of uPA or its membrane receptor UPAR; **plasminogen** activator inhibitors PAI-1 and PAI-2; metalloproteinases MMP-1, MMP-2, MMP-3, MMP-9 and membrane type MMP1; or tissue inhibitors of metalloproteinases TIMP-1 and TIMP-2. RA stimulated the association of t-PA with the external cell membrane surface, which could be inhibited by **heparin** sulphate but not by mannose sugars or chelators of divalent cations, consistent with a role for amphoterin. Our data indicate that RA can promote the malignant behavior of S-type neuroblastoma cells refractory to RA-mediated terminal differentiation by enhancing their basement membrane invasive

capacity. We suggest that this results from the action of a novel, RA-regulated mechanism involving stimulation of t-PA expression and its association with the cell membrane leading to increased PA-dependent matrix degradation.

L10 ANSWER 29 OF 56 MEDLINE DUPLICATE 8
ACCESSION NUMBER: 97288653 MEDLINE
DOCUMENT NUMBER: 97288653 PubMed ID: 9143604
TITLE: Upregulation of urokinase-type **plasminogen** activator by endogenous and exogenous HIV-1 Tat protein in **tumour** cell lines derived from BK virus/tat-transgenic mice.
AUTHOR: Rusnati M; Coltrini D; Campioni D; Tanghetti E; Corallini A; Barbanti-Brodano G; Giuliani R; Gibellini D; Presta M
CORPORATE SOURCE: Department of Biomedical Sciences and Biotechnology, University of Brescia, Italy.
SOURCE: AIDS, (1997 May) 11 (6) 727-36.
Journal code: 8710219. ISSN: 0269-9370.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals; AIDS
ENTRY MONTH: 199707
ENTRY DATE: Entered STN: 19970724
Last Updated on STN: 20000303
Entered Medline: 19970715

AB OBJECTIVE: To demonstrate that Tat modulates the **plasminogen** -dependent proteolytic activity of **tumour** cell lines derived from BK virus (BKV)/tat-transgenic mice by affecting the production of **plasminogen** activators (PA) and the PA inhibitor (PAI)-1 and to demonstrate that this occurs through mechanism(s) that are distinct from those responsible for transactivating activity of extracellular Tat. DESIGN AND METHODS: To assess whether endogenous Tat is responsible for PA activity in T53 adenocarcinoma cells, cell cultures were transfected with antisense Tat cDNA and evaluated for cell-associated PA activity by a **plasmin** chromogenic assay. The assay was also used to evaluate PA activity in T53 cells and T111 leiomyosarcoma cells stimulated by extracellular Tat. The type(s) of PA produced were identified by sodium dodecyl sulphate-polyacrylamide gel electrophoresis zymography. The levels of PAI-1 were evaluated by Western blotting. Tat transactivating activity was measured by a chloramphenicol acetyltransferase (CAT) enzyme-linked immunosorbent assay in HL3T1 cells containing integrated copies of an HIV-1 long terminal repeat (LTR)-CAT plasmid. RESULTS: Transfection of T53 cells with antisense Tat cDNA results in the decrease of Tat production and PA activity. Exogenously added Tat increases PA levels in T53 and in T111 cells. PA activity was identified as urokinase-type PA (uPA). Tat also increases the production of PAI-1 in T111 but not in T53 cells. Chloroquine and **heparin** have different affects on the LTR-CAT-transactivating and the PA-inducing activities of Tat. The fusion protein glutathione-S-transferase-Tat and the mutant Tat-1e, lacking the second Tat exon, cause LTR-CAT transactivation without stimulating uPA upregulation. CONCLUSIONS: Tat affects the fibrinolytic activity of **tumour** cell lines derived from BKV/tat-transgenic mice by modulating the production of both uPA and

PAI-1 via autocrine and paracrine mechanisms of action. The capacity of Tat to modulate the **plasminogen**-dependent proteolytic activity of these **tumour** cell lines may contribute to their metastatic potential. The uPA-inducing activity of Tat depends upon specific biological and structural features of the Tat protein that are distinct from those responsible for its LTR-CAT-transactivating activity, suggesting distinct mechanisms of induction for the two biological responses.

L10 ANSWER 30 OF 56 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 95316143 EMBASE
DOCUMENT NUMBER: 1995316143
TITLE: Matrix metalloproteinases and cardiovascular disease.
AUTHOR: Dollery C.M.; McEwan J.R.; Henney A.M.
CORPORATE SOURCE: Department of Medicine, Rayne Institute, Univ. College London Medical School, University St,London WC1E 6JJ, United Kingdom
SOURCE: Circulation Research, (1995) 77/5 (863-868). ISSN: 0009-7330 CODEN: CIRUAL
COUNTRY: United States
DOCUMENT TYPE: Journal; (Short Survey)
FILE SEGMENT: 005 General Pathology and Pathological Anatomy
018 Cardiovascular Diseases and Cardiovascular Surgery
029 Clinical Biochemistry
037 Drug Literature Index
LANGUAGE: English

L10 ANSWER 31 OF 56 JICST-EPlus COPYRIGHT 2003 JST
ACCESSION NUMBER: 940671022 JICST-EPlus
TITLE: Fluctuations of Tissue-Type **Plasminogen** ActivatorvPlasminogen Activator Inhibitor-1 Complex in Patients with DIC.
AUTHOR: NAGAIZUMI KEIKO; KUROSO KAZUKO; AMANO KAGEHIRO; SATO TAKESHI; FUKUTAKE KATSUYUKI; FUJIMAKI MICHIO
CORPORATE SOURCE: Tokyo Medical College
SOURCE: Rinsho Byori (Japanese Journal of Clinical Pathology), (1994) vol. 42, no. 7, pp. 707-712. Journal Code: Z0687A (Fig. 4, Tbl. 1, Ref. 17) CODEN: RBYOAI; ISSN: 0047-1860
PUB. COUNTRY: Japan
DOCUMENT TYPE: Journal; Article
LANGUAGE: Japanese
STATUS: New
AB Plasma levels of tissue-type **plasminogen** activator antigen(t-PA: Ag), **plasminogen** activator inhibitor-1 antigen(PAI-1: Ag), the active form of PAI-1 (active PAI) and t-PA v PAI-1 complex (PAI-C) were analyzed in 7 patients with disseminated intravascular coagulation (DIC) syndrome. The levels of t-PA: Ag and PAI-C decreased after amelioration of DIC in 6 patients whose underlying disease improved, but their PAI-1: Ag and active PAI showed various fluctuations. The levels of t-PA: Ag and PAI-C showed a good correlation of r=0.885. The levels of t-PA: Ag or PAI -C showed an inversed correlation with platelet counts, and correlations with the levels of **plasmin** .ALPHA.2PI complex, D dimer and E fragments of FDP. It was considered that plasma levels of PAI-C reflected levels of t-PA released from the endothelial cells, which was related to acceleration of fibrinolysis

in DIC patients with improved underlying disease. On the other hand, these levels remained high in a patient whose underlying disease did not improve after recovering from DIC. It was considered that the stimulation of endothelial cells by **cancer** cells continued to exert an effect. (author abst.)

L10 ANSWER 32 OF 56 MEDLINE DUPLICATE 9
ACCESSION NUMBER: 94231681 MEDLINE
DOCUMENT NUMBER: 94231681 PubMed ID: 8176840
TITLE: Anticoagulant and fibrinolytic systems of the injured vascular endothelial cells.
AUTHOR: Takeya H; Suzuki K
CORPORATE SOURCE: Department of Molecular Biology on Genetic Disease, Mie University School of Medicine, Tsu.
SOURCE: RINSHO BYORI. JAPANESE JOURNAL OF CLINICAL PATHOLOGY, (1994 Apr) 42 (4) 333-9. Ref: 23
Journal code: 2984781R. ISSN: 0047-1860.
PUB. COUNTRY: Japan
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LANGUAGE: Japanese
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199406
ENTRY DATE: Entered STN: 19940620
Last Updated on STN: 19940620
Entered Medline: 19940608

AB Recent advances in determining anti-thrombogenic functions of vascular endothelial cells are reviewed. The following anticoagulant and fibrinolytic systems of endothelial cells are physiologically important; (1) Endothelial cell-derived metabolites including prostacyclin and nitric oxide (NO) support platelet inactivity. (2) Antithrombin III and tissue factor pathway inhibitor (TFPI) bound to **heparin**-like proteoglycans on endothelial cell membrane inhibit activated serine protease coagulation factors such as thrombin, factor Xa and factor VIIa-tissue factor complex. (3) Thrombomodulin converts thrombin from procoagulant into anticoagulant. Thrombin associated to thrombomodulin on endothelial cells activates protein C. Activated protein C in concert with protein S bound to endothelial cell membrane inactivates factors Va and VIIIa. (4) A receptor for both tissue **plasminogen** activator and **plasminogen** on endothelial cells provides an efficient **plasmin** generating system. Perturbation of these anti-thrombogenic systems of endothelial cells is caused by endotoxin (LPS), cytokines such as interleukin-1 and **tumor** necrosis factor (TNF), and risk factors for atherogenesis including lipoprotein(a) and homocysteine may result in arterial or venous thrombosis with subsequent development of atherosclerosis.

L10 ANSWER 33 OF 56 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 94007754 EMBASE
DOCUMENT NUMBER: 1994007754
TITLE: 'Brain attack': The rationale for treating stroke as a medical emergency.
AUTHOR: Camarata P.J.; Heros R.C.; Latchaw R.E.; Piepgras D.G.; Whisnant J.P.; Smith R.R.
CORPORATE SOURCE: Department of Neurosurgery, UMHC, University of Minnesota, 420 Delaware St. S.E.,Minneapolis, MN

55455, United States
SOURCE: Neurosurgery, (1994) 34/1 (144-158).
ISSN: 0148-396X CODEN: NRSRDY
COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 005 General Pathology and Pathological Anatomy
008 Neurology and Neurosurgery
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English

AB STROKE IS THE third leading cause of death in the United States, behind only heart disease and **cancer**. With an estimated three million survivors of stroke in the United States, the cost to society, both directly in health care and indirectly in lost income, is staggering. Despite recent advances in basic and clinical neurosciences, which have the potential to improve the treatment of acute stroke, the general approach to the acute stroke patient remains one of therapeutic nihilism. Most basic science studies show that to be effective, acute intervention to reperfuse ischemic tissue must take place within the first several hours, as is the case with ischemic myocardium. In addition, most neuroprotective agents must also be administered within a short time frame to be effective at salvaging at-risk tissue. Recent studies have suggested that the outcome after intracerebral and subarachnoid hemorrhage is improved with early intervention. However, most stroke patients fail to present to medical attention within this short 'window of opportunity.' The public's knowledge about stroke is woefully inadequate. However, clinicians who deal with stroke can use the dramatic changes in the treatment of acute myocardial infarction over the last 2 decades as a guide for shaping changes in the management of acute stroke. Comprehensive educational efforts aimed at clinicians and the public at large have dramatically reduced the time from symptom onset to presentation and treatment for acute myocardial infarction, enabling treatment methods such as thrombolysis to be effective. The Decade of the Brain offers a unique opportunity to all concerned with the treatment of the patient with acute stroke to engage in a concerted effort to bring patients with a 'brain attack' to specialized neurological attention within the same timeframe that the 'heart attack' patient is handled. Such an effort is justified because, although at the present time there are few therapeutic interventions of 'proven' value in the treatment of acute stroke, there is more than sufficient suggestive evidence that a number of approaches may be beneficial within the first few hours after the onset of the stroke.

L10 ANSWER 34 OF 56 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V.

ACCESSION NUMBER: 95068291 EMBASE
DOCUMENT NUMBER: 1995068291
TITLE: Treatment of thromboembolic complications in patients with brain **tumors**.
AUTHOR: Norris L.K.; Grossman S.A.
CORPORATE SOURCE: Neuro-Oncology, Johns Hopkins Oncology Center, 600 North Wolfe Street,Baltimore, MD 21287, United States
SOURCE: Journal of Neuro-Oncology, (1994) 22/2 (127-137).
ISSN: 0167-594X CODEN: JNODD2
COUNTRY: United States
DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 008 Neurology and Neurosurgery

018 Cardiovascular Diseases and Cardiovascular Surgery
025 Hematology
037 Drug Literature Index
038 Adverse Reactions Titles

LANGUAGE: English
SUMMARY LANGUAGE: English

AB Thromboembolic disease is common in patients with malignant brain **tumors** and represents a major cause of morbidity and mortality in these patients. The presenting signs and symptoms of deep venous thrombosis and pulmonary emboli can be subtle: thus, a high index of suspicion is required to ensure a timely diagnosis. The accuracy of non-invasive studies of the lower extremities and lungs have significant limitations. Venography and pulmonary angiography remain the best diagnostic techniques when difficult decisions arise regarding the need for anticoagulants in these patients. Patients with malignant brain **tumors** can be safely anticoagulated with **heparin** and warfarin, if these agents are monitored carefully. Continuous intravenous infusions of **heparin** are associated with lower risks of bleeding than intermittent boluses. Clinicians may wish tn modify the recommended initial bolus dose of **heparin** in patients without life threatening thromboembolic disease. Warfarin reduces the incidence of recurrent thromboembolic events. The incidence of warfarin-related bleeding can be lowered without compromising efficacy by maintaining the PT ratio at 1.3. Potential warfarin drug interactions must be considered, aspirin containing medications and NSAIDS should be avoided, and the platelet count should be kept above 50,000 using transfusions if required to prevent potentially life-threatening bleeding in anticoagulated patients. Thrombolytics are contraindicated in this patient population. Vena caval filters and thrombectomy are rarely required. Additional research is needed tn determine the best techniques to prevent deep venous thrombosis and pulmonary embolism in patients with brain **tumors**.

L10 ANSWER 35 OF 56 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 94116343 EMBASE
DOCUMENT NUMBER: 1994116343
TITLE: Gene therapy for vascular diseases.
AUTHOR: Wu K.K.; Zoldhelyi P.; Willerson J.T.; Xu X.-M.; Loose-Mitchell D.S.; Wang - L.H.
CORPORATE SOURCE: Division of Hematology, University of Texas Medical School, 6431 Fannin Street,Houston, TX 77030, United States
SOURCE: Texas Heart Institute Journal, (1994) 21/1 (98-103). ISSN: 0730-2347 CODEN: THIJDO
COUNTRY: United States
DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 018 Cardiovascular Diseases and Cardiovascular Surgery
022 Human Genetics
025 Hematology
029 Clinical Biochemistry
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English

AB Gene transfer by virus- and liposome-mediated vectors has potential for treating genetic diseases, **cancer**, and cardiovascular

diseases. In this article, we discuss the general principle and techniques for gene transfer and the specific issues facing therapy for vascular diseases. We also propose a strategy for using virus-mediated gene transfer to restore the vasoprotective function of the vascular wall, thereby preventing vascular thrombosis. Experimental data from ongoing work in our laboratories are presented to illustrate the importance of this approach in vascular gene transfer therapy.

L10 ANSWER 36 OF 56 JICST-EPlus COPYRIGHT 2003 JST
ACCESSION NUMBER: 940090950 JICST-EPlus
TITLE: Coagulation and fibrinolysis activation in leukemia. 3. Time course of coagulation and fibrinolysis-related markers after chemotherapy in patients with acute myelocytic leukemia and malignant lymphoma.
AUTHOR: IHARA AKIHIRO; FURUBAYASHI TAKAYASU; ISHIKAWA KATSUNORI
CORPORATE SOURCE: Kure National Hospital
SOURCE: Iryo (Japanese Journal of National Medical Services), (1993) vol. 47, no. 12, pp. 931-936. Journal Code: F0707A (Fig. 4, Ref. 14)
CODEN: IRYOAV; ISSN: 0021-1699
PUB. COUNTRY: Japan
DOCUMENT TYPE: Journal; Article
LANGUAGE: Japanese
STATUS: New
AB In order to evaluate precisely the blood coagulation and fibrinolytic state of hematologically malignant diseases, we measured plasma levels of D-dimer, thrombin-antithrombin III complex (TAT), plasm-.ALPHA.2 **plasmin** inhibitor complex (PIC) and **plasminogen** activator inhibitor-1 antigen (PAI-1 antigen) by ELISA in 6 patients with acute myelocytic leukemia (AML) and in 6 patients with malignant lymphoma (ML) before and after chemotherapy. The mean plasma levels of TAT, D-dimer, PIC and PAI 1 antigen before therapy were 6.42.+-.2.77 ng/ml, 406.11.+-.237.54ng/ml, 1.31.+-.0.54 .MU.g/ml and 51.09.+-.39.0 ng/ml, respectively. These values were significantly higher than those in normal controls. The mean plasma levels of D-dimer, TAT and PIC at 24-48 hours after chemotherapy were remarkably higher than those before chemotherapy. The PAI-1 antigen levels were not changed at all after therapy. In most patient with AML, the plasma levels of D dimer, TAT and PIC were clearly increased at 24-48 hours after chemotherapy, but not in patients with ML. One patient with NHL who had remarkably higher levels of D-dimer, TAT and PIC than other patients with ML died of pulmonary embolism. In conclusion, anticoagulant therapy must be neccesary for patients with higher levels of D-dimer, TAT and PIC. (author abst.)

L10 ANSWER 37 OF 56 MEDLINE DUPLICATE 10
ACCESSION NUMBER: 93260040 MEDLINE
DOCUMENT NUMBER: 93260040 PubMed ID: 7684043
TITLE: Mechanism of action of angiostatic steroids: suppression of **plasminogen** activator activity via stimulation of **plasminogen** activator inhibitor synthesis.
AUTHOR: Blei F; Wilson E L; Mignatti P; Rifkin D B
CORPORATE SOURCE: Department of Pediatrics, New York University Medical

Center, New York, New York.
CONTRACT NUMBER: 5 T32 GM 07552 (NIGMS)
CA 34282 (NCI)
CA 49419 (NCI)
+
SOURCE: JOURNAL OF CELLULAR PHYSIOLOGY, (1993 Jun) 155 (3) 568-78.
Journal code: 0050222. ISSN: 0021-9541.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199306
ENTRY DATE: Entered STN: 19930625
Last Updated on STN: 20000303
Entered Medline: 19930617

AB Recently, a novel class of angiostatic steroids which block angiogenesis in several systems has been described. Since the elaboration of proteases is believed to be an important component of angiogenesis, we tested whether these steroids blocked the fibrinolytic response of endothelial cells to the angiogenic protein, basic fibroblast growth factor [bFGF]). Cultured bovine aortic endothelial (BAE) cells were incubated with bFGF and/or medroxyprogesterone acetate (MPA), an angiostatic steroid which has been shown to inhibit vascularization, collagenolysis, and **tumor** growth. When bFGF (3 ng/ml) was added to confluent monolayers of BAE cells, **plasminogen** activator (PA) activity in the medium was increased threefold. In contrast, MPA at 10(-6) M, 10(-7) M, 10(-8) M, and 10(-9) M decreased PA levels in the medium by 83%, 83%, 75%, and 39%, respectively. The stimulation of PA levels in BAE cells by bFGF (3 ng/ml) was abrogated by the presence of 10(-6) M MPA. This decrease in PA activity was found to be mediated by a significant increase in **plasminogen** activator inhibitor type-1 (PAI-1) production. MPA, therefore, negated one of the important enzymatic activities associated with the angiogenic process. In contrast to the decreased levels of secreted PA in cultures exposed simultaneously to MPA and bFGF, cell-associated PA levels remained high, consistent with earlier observations indicating that PAI-1 does not inhibit cell-associated PA. Thus, angiostatic steroids may exert their inhibitory effects on angiogenesis by increasing the synthesis of PAI-1. This, in turn, inhibits PA activity and, therefore, **plasmin** generation, which is essential for the invasive aspect of angiogenesis.

L10 ANSWER 38 OF 56 MEDLINE DUPLICATE 11
ACCESSION NUMBER: 92164535 MEDLINE
DOCUMENT NUMBER: 92164535 PubMed ID: 1371448
TITLE: Involvement of the **plasmin** system in dissociation of the insulin-like growth factor-binding protein complex.
AUTHOR: Campbell P G; Novak J F; Yanosick T B; McMaster J H
CORPORATE SOURCE: Allegheny-Singer Research Institute, Orthopedic Research Laboratory, Pittsburgh, Pennsylvania 15212.
SOURCE: ENDOCRINOLOGY, (1992 Mar) 130 (3) 1401-12.
Journal code: 0375040. ISSN: 0013-7227.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)

LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 199204
ENTRY DATE: Entered STN: 19920417
Last Updated on STN: 19970203
Entered Medline: 19920402

AB A variety of treatments, including acid, **heparin**, and proteases, are known to free insulin-like growth factors (IGFs) from their binding proteins (IGFBPs). However, the physiologically relevant mechanism regulating the interaction of IGFs and IGFBPs is unknown. We report here the ability of **plasmin** to dissociate IGFs from IGFBPs. In chromatographic experiments, **plasmin** completely dissociated complexes of [125I] IGF-I-BP and [125I]IGF-II-BP formed with purified decidual IGFBP (hIGFBP-1) or IGFBPs present in medium conditioned by human osteosarcoma MG-63 cells. **Plasmin** dissociation of IGF-BP complexes was dose dependent. Neither **plasminogen** nor **plasminogen** activators (PAs) alone affected dissociation; however, activation of **plasminogen** to **plasmin** by either urokinase PA or tissue-type PA resulted in the dissociation of IGF-BP complexes. **Plasmin** dissociated immunoreactive and bioactive IGF from IGFBP equivalent to approximately 70% and approximately 60% of the acid control value, respectively. In medium conditioned by MG-63 cells, dissociation of IGF-BP complexes was catalyzed by PAs secreted by MG-63 cells, principally urokinase PA. Limited **plasmin** degradation of IGF was suggested by chromatographic experiments involving [125I] IGF. Treatment of uncomplexed IGF-I with **plasmin** concentrations equivalent to those in chromatographic experiments did not result in a significant loss of bioactivity, although a 2-fold increase in the **plasmin** concentration resulted in a approximately 20% loss of activity. Similar **plasmin** treatment of equimolar concentrations of hIGFBP-1 resulted in a marked degradation of IGFBP, with loss of IGF-binding ability. In vitro experiments confirmed **plasmin** dissociation of bioactive IGF-I from hIGFBP-1. In MG-63 cells, IGFBPs can form an IGF reservoir in the pericellular space surrounding the cells by combining IGFs with IGF-BP to form complexes that are incapable of binding to the IGF receptors. The secretion of PAs by osteosarcoma cells and the availability of **plasminogen** in the extravascular tissues indicate the possibility of a regulatory system in osteosarcoma cells in which pericellular **plasmin** affects the availability of IGFs to their membrane receptors.

L10 ANSWER 39 OF 56 SCISEARCH COPYRIGHT 2003 THOMSON ISI
ACCESSION NUMBER: 92:226647 SCISEARCH
THE GENUINE ARTICLE: HL749
TITLE: VITRONECTIN IN LIVER DISORDERS - BIOCHEMICAL AND IMMUNOHISTOCHEMICAL STUDIES
AUTHOR: INUZUKA S (Reprint); UENO T; TORIMURA T; TAMAKI S; SAKATA R; SATA M; YOSHIDA H; TANIKAWA K
CORPORATE SOURCE: KURUME UNIV, SCH MED, DEPT INTERNAL MED 2, 67 ASAHI MACHI, KURUME, FUKUOKA 830, JAPAN (Reprint)
COUNTRY OF AUTHOR: JAPAN
SOURCE: HEPATOLOGY, (APR 1992) Vol. 15, No. 4, pp. 629-636. ISSN: 0270-9139.
DOCUMENT TYPE: Article; Journal
FILE SEGMENT: LIFE; CLIN

LANGUAGE: ENGLISH
REFERENCE COUNT: 53

ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB The concentration of plasma vitronectin was determined and compared with various parameters of liver function including the blood coagulation system in patients with liver diseases. The severity of cirrhosis was graded according to Child's criteria and compared with the plasma vitronectin level. Furthermore, the distribution of vitronectin in the liver of patients with liver diseases was studied by light and electron microscopy using the indirect immunoperoxidase method.

The plasma vitronectin level was low in all liver disease groups as compared with the healthy controls. The difference from the controls was significant in patients with hepatocellular **carcinoma** and decompensated cirrhosis. Moreover, the plasma vitronectin level was positively correlated with the levels of serum cholinesterase, albumin, plasma alpha(2) **plasmin** inhibitor-**plasmin** complex and the prothrombin time and results of the hepatoplastin test. Plasma vitronectin decreased with increasing severity of cirrhosis according to Child's criteria. These results suggest that the plasma vitronectin level is a useful parameter of hepatic synthetic function in patients with liver diseases; it may also reflect the severity of cirrhosis.

Light microscopy revealed vitronectin in the area of focal necrosis and the portal tracts in the liver of patients with acute viral hepatitis, in the area of piecemeal necrosis in the liver of patients with chronic hepatitis and along the area of fiber deposition in the liver of patients with cirrhosis. Immunoelectron microscopy showed vitronectin in the rough endoplasmic reticulum of hepatocytes. Moreover, vitronectin was seen around inflammatory cells, endothelial cells, Ito cells and hepatocytes in the perisinusoidal area near focal necrosis and piecemeal necrosis and on collagen fibers.

These results suggest that vitronectin may be produced by hepatocytes and that they play an important role as an extracellular matrix component in the injured liver.

L10 ANSWER 40 OF 56 SCISEARCH COPYRIGHT 2003 THOMSON ISI
ACCESSION NUMBER: 92:669550 SCISEARCH
THE GENUINE ARTICLE: JX880
TITLE: CLINICAL-TRIALS WITH ANTICOAGULANT AND ANTIPLATELET THERAPIES
AUTHOR: ZACHARSKI L R (Reprint); MEEHAN K R; ALGARRA S M; CALVO F A
CORPORATE SOURCE: DEPT VET AFFAIRS MED & REGIONAL OFF CTR, WHITE RIVER JCT, VT, 05009 (Reprint); DARTMOUTH COLL, HITCHCOCK MED CTR, DARTMOUTH MED SCH, DEPT MED, HANOVER, NH, 03756; CLIN UNIV NAVARRA, DEPT ONCOL, E-31080 PAMPLONA, SPAIN; HAHNEMANN UNIV, SCH MED, DEPT RADIAT ONCOL, PHILADELPHIA, PA, 19102
COUNTRY OF AUTHOR: USA; SPAIN
SOURCE: CANCER AND METASTASIS REVIEWS, (NOV 1992) Vol. 11, No. 3-4, pp. 421-431.
ISSN: 0167-7659.
DOCUMENT TYPE: General Review; Journal
FILE SEGMENT: LIFE
LANGUAGE: ENGLISH
REFERENCE COUNT: 72

ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB Clinical trials of drugs that influence coagulation and fibrinolysis pathways have been undertaken in patients with malignancy because these pathways are capable of influencing malignant progression. The validity of this concept was originally confirmed in experimental animal models of malignancy. Earlier pilot studies in human disease have been succeeded by definitive prospective randomized clinical trials that have revealed heterogeneity of responsiveness to anticoagulant and fibrinolytic agents that may be attributable to differences in mechanisms of interaction of the **tumor** cells of various types of malignancy with these pathways in vivo. In certain **tumor** types studied thus far, increased **tumor** response rates and prolongation of survival have been observed that suggest the possibility that substantial benefit may be realized from this treatment approach in patients with malignancy. In addition, the availability of newer and potentially more effective therapeutic agents holds promise for even greater gains in previously tested **tumor** types. The ability to design treatment regimens that correspond to defined mechanisms that pertain to specific **tumor** types should permit future studies to be designed rationally. Current data suggest that anticoagulant and fibrinolytic agents might reasonably be tested in **tumor** types characterized by the existence of a **tumor** cell-associated coagulation pathway with thrombin generation and conversion of fibrinogen to fibrin (such as small cell **carcinoma** of the lung). By contrast, protease inhibitors might reasonably be tested in **tumor** types characterized by expression of **tumor** cell **plasminogen** activators. Expansion of current views on the possible role of antithrombic drugs in **cancer** therapy is justified. For example, antithrombotic drugs classified as non-steroidal anti-inflammatory agents may inhibit **carcinogenesis** while polyanionic drugs with anticoagulant properties, such as suramin and **heparin**, may inhibit growth factor interactions with cells. Intriguing new opportunities clearly exist for interactions between clinical and basic investigators that may provide both novel biologic insights and improved patient care.

L10 ANSWER 41 OF 56 SCISEARCH COPYRIGHT 2003 THOMSON ISI
ACCESSION NUMBER: 92:426345 SCISEARCH
THE GENUINE ARTICLE: JD066
TITLE: MODULATION OF THE CELL BINDING PROPERTY OF SINGLE CHAIN UROKINASE-TYPE **PLASMINOGEN**-ACTIVATOR BY NEUTROPHIL CATHEPSIN-G
AUTHOR: LEARMONTH M P; LI W; NAMIRANIAN S; KAKKAR V V; SCULLY M F (Reprint)
CORPORATE SOURCE: THROMBOSIS RES INST, EMMANUEL KAYE BLDG, MANRESA RD, LONDON SW3 6LR, ENGLAND
COUNTRY OF AUTHOR: ENGLAND
SOURCE: FIBRINOLYSIS, (1992) Vol. 6, Supp. 4, pp. 113-116. ISSN: 0268-9499.
DOCUMENT TYPE: Article; Journal
FILE SEGMENT: LIFE
LANGUAGE: ENGLISH
REFERENCE COUNT: 37

ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB Cathepsin G, a major proteolytic component of the neutrophil,

acted on single-chain urokinase **plasminogen** activator (sc-uPA) to generate a two chain form linked by disulphide bridges that was indistinguishable from **plasmin** generated tc-uPA by SDS-PAGE. Sequence analysis revealed that the cleavage site was located between 159Ile and 160Ile, as has previously been reported for elastase cleavage (Schmitt et al. 1989). A component (approximately 20%) was found to have been cleaved between 158Lys and 159Ile, the **plasmin** cleavage site and some **plasminogen** activating activity was found in the incubation mixture. A recombinant form of sc-uPA (rsc-uPA 158Glu) was cleaved by cathepsin G but not **plasmin**. Cathepsin G action has also been studied in the presence of **heparin**, as a model for possible modes of interaction in the presence of the ECM. Cleavage to two chain form was mediated in a dose dependent form and there was an accumulation of a modified single chain form which migrated just below sc-uPA on SDS-PAGE. Sequence analysis indicated cleavages between 23Lys-24Tyr and 25Phe-26Ser. These correspond to cleavages in the cell-binding (EGF-like) domain (Appella et al. 1987) and result in a loss of cell binding activity. The cathepsin G modified sc-uPA was converted to a two chain form by **plasmin** . We propose that cathepsin G may have a role in vivo in disrupting the cell surface activation of sc-uPA by destroying its ability to bind to the cell receptor.

L10 ANSWER 42 OF 56 MEDLINE DUPLICATE 12
ACCESSION NUMBER: 92005257 MEDLINE
DOCUMENT NUMBER: 92005257 PubMed ID: 1913515
TITLE: Inhibition of **tumor** implantation at sites of trauma by **plasminogen** activators.
AUTHOR: Murthy M S; Summaria L J; Miller R J; Wyse T B; Goldschmidt R A; Scanlon E F
CORPORATE SOURCE: Cell Biology Laboratory, Evanston Hospital, IL 60201.
SOURCE: CANCER, (1991 Oct 15) 68 (8) 1724-30. Journal code: 0374236. ISSN: 0008-543X.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 199110
ENTRY DATE: Entered STN: 19920124
Last Updated on STN: 19980206
Entered Medline: 19911029

AB The authors report on the influence of **plasminogen** activators (PA) on implantation of TA3Ha mammary **tumor** cells in the healing hepatic wounds of syngeneic strain A mice. Intravenously injected TA3Ha cells, although they rarely metastasize to the liver, formed **tumors** in the hepatic wounds of a significant percent (42%, P less than 0.0001) of mice. The frequency of **tumor** formation declined as the interval between surgery and **tumor** cell inoculation was increased. Furthermore, preexposure of cells to fibrinogen, fibronectin, laminin, or peptides containing the arginine-glycine-aspartic acid-serine residues dramatically reduced the frequency of **tumor** formation in the hepatic wounds. These results indicate that TA3Ha cells interact with fibrinogen-related proteins in the wound to aid their attachment and growth. Because these proteins are susceptible to digestion by **plasmin**, PA were used in this study to examine whether administration of these drugs

to the mice would modulate **tumor** formation in the liver wounds. Among the PA tested, human **plasmin** B-chain-streptokinase complex (B-SK) and recombinant tissue **plasminogen** activator (t-PA) inhibited **tumor** implantation in a dose-related manner. Administration of 900 units (U) of B-SK or 3300 U of t-PA per mouse reduced the frequency of **tumor** formation from 42% to 0% (P = 0.02) and 11% (P = 0.02), respectively. The B-SK was complexed with p-nitrophenyl-p-guanidinobenzoate; it did not activate the **plasminogen** or inhibit **tumor** formation in the hepatic wounds. Although urokinase activated the **plasminogen**, it did not inhibit **tumor** implantation in the hepatic wound. **Heparin**, an anticoagulant that prevents conversion of fibrinogen to fibrin without being fibrinolytic, had no influence on **tumor** formation in the hepatic wounds. The PA can generate **plasmin** that digests the cell attachment proteins in wounds and consequently inhibits **tumor** cell attachment.

L10 ANSWER 43 OF 56 MEDLINE DUPLICATE 13
ACCESSION NUMBER: 92179720 MEDLINE
DOCUMENT NUMBER: 92179720 PubMed ID: 1839080
TITLE: Stimulation of cell surface **plasminogen** activation by **heparin** and related polyionic substances.
AUTHOR: Stephens R W; Pollanen J; Tapiovaara H; Woodrow G; Vaheri A
CORPORATE SOURCE: Department of Virology, University of Helsinki, Finland.
SOURCE: SEMINARS IN THROMBOSIS AND HEMOSTASIS, (1991 Jul) 17 (3) 201-9.
Journal code: 0431155. ISSN: 0094-6176.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199204
ENTRY DATE: Entered STN: 19920424
Last Updated on STN: 20000303
Entered Medline: 19920408

AB The functional operation of the cell surface pro-u-PA and **plasminogen** activating system has previously been shown to depend on the assembly of u-PA receptors, **plasminogen** binding sites, and their respective ligands at the focal adhesions of cell extensions. We now show that additional factors operate that affect the persistence of functional activity and that evidently involve charge interactions mediated by polyanions, such as those found in the cell surface proteoglycans. **Heparin** -like compounds and protamine were identified as fast-acting stimulators of cell surface **plasminogen** activation. **Heparin** stabilized surface u-PA activity during **plasminogen** activation, and we propose that a **heparin** binding site exists in the kringle structure of u-PA. **Heparin** at 40 micrograms/ml could reduce u-PA loss to only 20% compared with 60% on control cells activating **plasminogen**. Protamine (25 micrograms/ml) exerted a strong stimulatory effect on the level of generated bound **plasmin** and notably prolonged the persistence of this activity, so that 100

minutes after addition of **plasminogen** the level of **plasmin** on protamine-treated cells was five times higher than on control-treated cells. The effect of protamine on **plasmin** clearance suggests that an unknown **plasmin** inhibitor may be produced by rhabdomyosarcoma cells, whose action is accelerated by endogenous polyanions, in an analogous manner to thrombin inactivation by antithrombin III and protease nexin on endothelial cells and fibroblasts, respectively. The stimulatory effects of **heparin** and protamine do not affect the inactivation of cell surface u-PA by recombinant PAI-2.

L10 ANSWER 44 OF 56 MEDLINE DUPLICATE 14
ACCESSION NUMBER: 91315445 MEDLINE
DOCUMENT NUMBER: 91315445 PubMed ID: 1830477
TITLE: Binding of one-chain tissue-type **plasminogen** activator to fibrin, partially **plasmin** -degraded fibrin, lysine and **heparin**.
AUTHOR: Fischer B
CORPORATE SOURCE: Research Center of Biotechnology, Central Institute of Molecular Biology, Department Enzymology, Berlin-Buch, FRG.
SOURCE: BIOMEDICA BIOCHIMICA ACTA, (1991) 50 (1) 47-54. Journal code: 8304435. ISSN: 0232-766X.
PUB. COUNTRY: GERMANY: Germany, Federal Republic of
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199108
ENTRY DATE: Entered STN: 19910913
Last Updated on STN: 19980206
Entered Medline: 19910829

AB Tissue-type **plasminogen** activator (t-PA) binds to **heparin** with an association constant of 2.4 x 10(4) l/mol at pH 7.4. The binding increases at lower pH-values and reaches maximal values below pH 6.0. Sodium chloride above 0.5 mol/l abolishes t-PA binding to **heparin** at neutral pH. t-PA binds to lysine maximally at pH 6 to pH 9. At neutral pH the association constant is 1.8 x 10(5) l/mol. Sodium chloride concentrations of 1 mol/l reduce interaction of the enzyme to lysine by about 60% at pH 7.4. Binding of t-PA to fibrin and to partially **plasmin**-degraded fibrin takes place maximally at pH 6 to 9. The interaction of t-PA with **plasmin**-degraded fibrin is less sensitive to addition of lysine than the interaction of t-PA and fibrin. Sodium chloride concentrations of 1 mol/l reduce the interaction of t-PA to fibrin by about 60% at pH 7.4.

L10 ANSWER 45 OF 56 CANCERLIT
ACCESSION NUMBER: 92686356 CANCERLIT
DOCUMENT NUMBER: 92686356
TITLE: SERINE PROTEASES AND THEIR SERPIN INHIBITORS IN THE NERVOUS SYSTEM: REGULATION IN DEVELOPMENT AND IN DEGENERATIVE AND MALIGNANT DISEASE.
AUTHOR: Anonymous
CORPORATE SOURCE: No affiliation given.
SOURCE: NATO ASI Ser A, (1990) 191 1-359.
DOCUMENT TYPE: Book; (MONOGRAPH)
LANGUAGE: English
FILE SEGMENT: Institute for Cell and Developmental Biology

ENTRY MONTH: 199210
ENTRY DATE: Entered STN: 19941107
Last Updated on STN: 19970509

AB This book contains the proceedings of a NATO Advanced Research Workshop, held in Maratea, Italy, on the effects of serine proteases and their serpin inhibitors in the nervous system on regulation in development and in degenerative and malignant disease. In what is intended as a reference book in the field of protease regulation in neurobiological situations, experts in the biochemistry and molecular biology of fibrinolysis and protease inhibition and those in neurobiology addressed sessions on biochemistry, cell biology and molecular biology of serine proteases and serpins; serine proteases in the nervous system; balance of proteases and serpins in the nervous system; and serpins in degenerative and malignant neurologic diseases. Topics presented included the following: the receptor for urokinase **plasminogen** activator as a key molecule dictating and regulating surface **plasmin** formation, regulation of tissue **plasminogen** activator secretion from human endothelial cells, structure and function of tissue-type **plasminogen** activator, polypeptide chain structure of inter-alpha-trypsin inhibitor and pre-alpha-trypsin inhibitor (evidence for chain assembly by glycan and comparison with other 'kunin'-containing proteins), induction of the urokinase-type **plasminogen** activator gene by cytoskeleton-disrupting agents, signal transduction chains involved in the control of the fibrinolytic enzyme cascade, structure of the human protease nexin (PN) gene and expression of recombinant forms of PN-I, presence and significance of alpha 1-antitrypsin in human brain **tumors** and roles of serpins in pathogenesis of brain **tumors**.

L10 ANSWER 46 OF 56 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 88240032 EMBASE
DOCUMENT NUMBER: 1988240032
TITLE: Marked potentiation of the plasminogenolytic activity of pro-urokinase by unfractionated **heparin** and a low molecular-weight **heparin**.
AUTHOR: Dosne A.M.; Bendetowicz A.V.; Kher A.; Samama M.
CORPORATE SOURCE: Lab. Immunopharmacologie Exptle, CNRS UA-579, Paris, France
SOURCE: Thrombosis Research, (1988) 51/6 (627-630).
ISSN: 0049-3848 CODEN: THBRAA
COUNTRY: United States
DOCUMENT TYPE: Journal
FILE SEGMENT: 025 Hematology
030 Pharmacology
037 Drug Literature Index
LANGUAGE: English

L10 ANSWER 47 OF 56 MEDLINE DUPLICATE 15
ACCESSION NUMBER: 88274520 MEDLINE
DOCUMENT NUMBER: 88274520 PubMed ID: 3134521
TITLE: Further characterization of malignant glioma-derived vascular permeability factor.
AUTHOR: Criscuolo G R; Merrill M J; Oldfield E H
CORPORATE SOURCE: Surgical Neurology Branch, National Institute of Neurological and Communicative Disorders and Stroke, Bethesda, Maryland.
SOURCE: JOURNAL OF NEUROSURGERY, (1988 Aug) 69 (2) 254-62.

Journal code: 0253357. ISSN: 0022-3085.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 198808
ENTRY DATE: Entered STN: 19900308
Last Updated on STN: 19980206
Entered Medline: 19880817

AB The nature of vascular permeability factor (VPF) activity derived from serum-free conditioned medium containing cultured human malignant glial **tumors** has been further investigated. A 1000-fold purification was accomplished by sequential **heparin**-Sepharose affinity chromatography and high-performance liquid chromatography gel filtration chromatography steps. Vascular permeability factor activity falls into a molecular weight range of 41,000 to 56,000 D. Activity is bound to hydroxylapatite, carboxymethyl-Sepharose, phenyl-Sepharose, and **heparin**-Sepharose, whereas little or no activity was bound to diethylaminoethyl-Sephacel. Vascular permeability factor activity is trypsin- and pepsin-sensitive but is unaffected by treatment with ribonuclease A. This suggests that VPF is a hydrophobic, positively charged (cationic) polypeptide with a potentially biologically significant affinity for **heparin**. As most proteins are negatively charged (anionic) and have no affinity for **heparin**, a significant advantage was gained by performing these purification steps. The activity of VPF is not inhibited by coinjection of conditioned medium with soybean trypsin inhibitor; or hexadimethrine (both known antagonists of tissue **plasminogen** activator, Hageman factor, and serum kallikrein); or aprotinin (an antagonist of both **plasmin** and tissue kallikrein); or phenylmethanesulfonyl fluoride (a serine esterase (elastase) inhibitor); or pepstatin-A (an acid protease inhibitor which inactivates vascular permeability-inducing leukokinins). These data, together with the fact that VPF is produced and released into serum-free media, provides substantial evidence against it being one of the more commonly known serum-derived permeability mediators. Treatment with dithiothreitol inhibited VPF activity, indicating the presence of at least one essential disulfide bond in this molecule. Inhibition by dexamethasone of VPF expression in cultured malignant glial cells appears to be selective. Dexamethasone-induced inhibition of VPF was dose-responsive and was not associated with a parallel inhibition of cellular protein synthesis as determined by tritiated leucine incorporation into trichloroacetic acid-precipitable material. Inclusion of dexamethasone in the culture medium was not associated with altered cell viability or cell number. A series of in vivo studies confirmed the inhibition of VPF activity in test animals pretreated with dexamethasone. This steroid-induced inhibition was partially reversed by treatment of test animals with actinomycin D prior to exposure to dexamethasone.(ABSTRACT TRUNCATED AT 400 WORDS)

L10 ANSWER 48 OF 56 MEDLINE DUPLICATE 16
ACCESSION NUMBER: 86252753 MEDLINE
DOCUMENT NUMBER: 86252753 PubMed ID: 2425022
TITLE: Studies on fibrinolysis and ascites accumulation associated with peritonitis **carcinomatosa**

--effects of protease inhibitors (PI) on MM2 ascites **tumor** growth, ascites accumulation and fibrinolysis.
AUTHOR: Shibata J
SOURCE: NIPPON SANKA FUJINKA GAKKAI ZASSHI. ACTA OBSTETRICA ET GYNAECOLOGICA JAPONICA, (1986 May) 38 (5) 719-27. Journal code: 7505749. ISSN: 0300-9165.
PUB. COUNTRY: Japan
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: Japanese
FILE SEGMENT: Priority Journals
ENTRY MONTH: 198607
ENTRY DATE: Entered STN: 19900321
Last Updated on STN: 19900321
Entered Medline: 19860728

AB The effects of protease inhibitors(PI), t-AMCHA, gabexate, aprotinin and **heparin** on the growth of mouse MM2 ascites **tumor** (MAT) and on several components of fibrinolysis were studied. The drugs were administered intraperitoneally one time daily for 12 days, one day after the **tumor** transplant. The volumes of ascites, total packed cell volume (TPCV) and fibrinolytic parameters (FDP, whole **plasmin**, **plasminogen** activator (PA)) were measured on the 8, 10 and 12th days of therapy. Fibrinolytic activity was assayed by the lysin sepharose affinity chromatography-radio caseinolytic method. Fibrinolytic activity in the ascites increased during the **tumor** growth. The ascites accumulation as well as levels of FDP, whole **plasmin** and PA in the drug treated group were significantly decreased when compared to the control group. In these drug-treated groups, MAT cells agglutinated in the abdominal cavity, but in contrast to this, no agglutination was observed in the control group. It was uncertain whether PI directly inhibited **tumor** growth. The fact that PI inhibited the ascites accumulation and also decreased fibrinolytic activity suggest the involvement of protease in the **neoplastic** process and indicates another therapeutic approach to malignant ascites **tumors**.

L10 ANSWER 49 OF 56 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER: 1987:108646 BIOSIS
DOCUMENT NUMBER: BA83:57624
TITLE: STUDIES ON THE MEDICAL TREATMENT OF DEEP VEIN THROMBOSIS.
AUTHOR(S): SCHULMAN S
CORPORATE SOURCE: DEP. MED., HUDDINGE HOSP., STOCKHOLM, SWED.
SOURCE: ACTA MED SCAND SUPPL, (1985 (RECD 1986)) 0 (704), 1-68.
CODEN: AMSSAQ. ISSN: 0365-463X.
FILE SEGMENT: BA; OLD
LANGUAGE: English

AB The aim of these studies was to investigate different regimens of thrombolytic therapy and oral anticoagulation, and to evaluate the effects of streptokinase (SK), **heparin** and warfarin in the treatment of deep vein thrombosis (DVT). Low-dose SK, although controlled according to the fibrinogen levels, did not provide improved thrombolysis compared to conventional high-dose SK, and more postthrombotic changes were registered after an average of 3 years. Furthermore, serious hemorrhagic side-effects occurred, which

makes this regimen inexpedient. Various regimens of local venous infusion of SK were tried, and with a dose of 4,000 IU/h for 72 h in combination with **heparin** a thrombolytic effect was achieved, albeit not greater than usually observed with conventional SK. Systemic hypofibrinogenemia and hemorrhage were not avoided. A hitherto not described side-effect with bullous dermatitis was reported. Venographic severity of calf vein thrombosis displayed a statistically significant correlation to long-term hemodynamic changes, as assessed with foot volumetry, after an average of 5 years. This correlation was stronger for the size of the thrombus after initial treatment than for the size at diagnosis. Thus it seems important to treat calf vein thrombosis with **heparin** in order to limit the extent of the thrombus, thereby reducing long-term sequelae. During **heparin** treatment, an average reduction of the thrombi of 17% was observed. This reduction was significantly correlated to a short duration of symptoms but not to parameters of **heparin** therapy or fibrinolytic components. However, patients with substantial thrombolysis had high **plasmin**-.alpha.2-antiplasmin (PAP) levels, and those with high tissue **plasminogen** activator (t-PA) inhibitor levels and remarkably also those with high t-PA antigen levels had no lysis. The concentration of t-PA antigen showed a significant increase during **heparin** infusion, whereas that of PAP and t-PA inhibitor was not influenced. By applying more intensive initial oral anticoagulation, stable therapeutic prothrombin time (PT)-levels were achieved one day earlier and the duration of **heparin** infusion could be equally reduced compared to the conventional regimen (4.4-5 days vs 5.4-6 days). The activity of coagulation factors II, VII, IX and X had dropped to the same level with both regimens the day **heparin** was discontinued, thromboembolic complications did not occur and no difference in bleeding was observed. The effectiveness of oral anticoagulation after DVT was studied in 596 patients treated for a total of 4450 months. Thromboembolic complications (n = 36) during long-term prophylaxis with oral anticoagulants following DVT occurred throughout the entire therapeutic range in patients with **cancer**, but never below a PT-level of 27% as assessed with Simplastin A (International Normalized Ratio (INR) > 1.9) among those without **neoplastic** disease. This confirmed that the limit of the therapeutic range, determined by the risk of thromboembolic complications, should be set at a Simplastin A-level of approx 25% (INR = 2.0) in prophylaxis of venous thrombosis. In a randomized comparison of our routine duration of oral anticoagulation and 50% reduction thereof, with stratification according to the nature of risk factors, no differences in thromboembolic complications could be detected. Experiences from this study will be used in a larger trial to establish the optimal duration of treatment.

L10 ANSWER 50 OF 56 CANCERLIT
ACCESSION NUMBER: 85608786 CANCERLIT
DOCUMENT NUMBER: 85608786
TITLE: INTERACTION OF **TUMOR** CELLS WITH THE BASEMENT MEMBRANE OF ENDOTHELIUM.
AUTHOR: Liotta L A; Goldfarb R H
CORPORATE SOURCE: Lab. of Pathology, Section of Tumor Invasion and Metastasis, NCI, NIH, Bethesda, MD 20205.
SOURCE: Dev Oncol, (1984) 22 319-41.

DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
LANGUAGE: English
FILE SEGMENT: Institute for Cell and Developmental Biology
ENTRY MONTH: 198505
ENTRY DATE: Entered STN: 19941107
Last Updated on STN: 19941107

AB Functional roles of various structural components of basement membranes (BMs) are described in relation to **tumor** cell-BM interaction at the levels of attachment, degradation, and locomotion. Purified proteinase-derived fragments of laminin were used to map the binding domains of the cross-shaped laminin molecule. The receptor for metastatic cells binds to a proteinase-resistant, disulfide-bonded intersection region of the three short arms, and the globular end regions of the three short arms bind to type IV BM collagen. The long arm binds to **heparin** sulfate proteoglycan. A proteinase-derived fragment of laminin, C1, binds to the receptor, and blocks **tumor** cell attachment in vitro and iv metastasis in vivo. **Tumor** cell-derived proteolytic enzymes, including type IV collagenase, type V collagenase, **plasminogen** activator, and **plasmin**, mediate BM degradation. Purified **tumor** cathepsin B-like proteinase appears to be capable of cleaving both the long arm of laminin and fibronectin. The C5a-derived **tumor** cell chemotactic peptide N-formyl-methionyl-leucyl-phenylalanine significantly stimulated migration of invasive, metastatic M5076 cells through amnion connective tissue at a concentration similar to that which was optimal for stimulating the migration of phagocytes and **tumor** cells across artificial porous filters. Understanding of the mechanisms of **tumor** cell attachment, dissolution, and locomotion with respect to the BM may yield critical insights into the early diagnosis of micrometastatic disease and into identification of rationales for treatment or prevention. (138 Refs)

L10 ANSWER 51 OF 56 MEDLINE DUPLICATE 17
ACCESSION NUMBER: 84032695 MEDLINE
DOCUMENT NUMBER: 84032695 PubMed ID: 6579053
TITLE: Evidence that a variety of cultured cells secrete protease nexin and produce a distinct cytoplasmic serine protease-binding factor.
AUTHOR: Eaton D L; Baker J B
CONTRACT NUMBER: CA-12306 (NCI)
SOURCE: JOURNAL OF CELLULAR PHYSIOLOGY, (1983 Nov) 117 (2) 175-82.
Journal code: 0050222. ISSN: 0021-9541.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 198312
ENTRY DATE: Entered STN: 19900319
Last Updated on STN: 19970203
Entered Medline: 19831221

AB Four criteria were used to examine serum-free conditioned cell culture medium for protease nexin (PN):(1) formation of SDS-stable approximately 77 K Da complexes between a medium component and [125I]thrombin; (2) acceleration by **heparin** of the rate of

formation of these complexes; (3) cellular binding of these complexes; and (4) inhibition by **heparin** of the cellular binding of complexes. Listed in order of decreasing PN production, PN was detected in media conditioned by the following cell types: human foreskin fibroblasts (0.18 micrograms/10(6) cells), rat embryo heart muscle cells (0.13 micrograms/10(6) cells), mouse myotubes (0.1 micrograms/10(6) cells), monkey kidney epithelial cells, human fibrosarcoma cells, human lung fibroblasts, simian virus 40 (SV-40)-transformed human fibroblasts, human epidermoid **carcinoma** cells, bovine aortic endothelial cells (only after phorbol ester treatment), and mouse myoblasts. No PN was found in medium conditioned by mouse 3T3 cells, SV40 virus-transformed 3T3 cells, human lymphoblasts, or mouse leukemia cells. Eleven of the cell types examined for secretion of PN were also examined for the presence of cytoplasmic thrombin-binding factors. Lysates from all of these cell types contained a factor that formed approximately 60-65 K Da sodium dodecyl sulfate (SDS)-stable complexes with [125I] thrombin. This MW is significantly lower than that of [125I] thrombin-PN complexes, indicating that the factor is distinct from PN. Nevertheless, PN and the cytoplasmic factor share similarities. Production of both PN (by HF cells and WI-26 cells) and the cytoplasmic factor (by HF cells and 3T3 cells) are stimulated by epidermal growth factor and phorbol myristate acetate. Also, both PN and the cytoplasmic factor complex trypsin, **plasmin**, urokinase, and thrombin, but not pancreatic elastase. Because a number of the cells that produce PN or the cytoplasmic serine protease-binding factor are known to produce **plasminogen** activators, both PN and the cytoplasmic factor could regulate **plasminogen** activator activity.

L10 ANSWER 52 OF 56 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER: 1982:143931 BIOSIS
DOCUMENT NUMBER: BA73:3915
TITLE: **HEPARIN** ENHANCES FIBRINOLYSIS IN B-16 MOUSE MELANOMA CELLS.
AUTHOR(S): HEANEY-KIERAS J; KIERAS F J
CORPORATE SOURCE: DEP. DERMATOL., NEW YORK UNIV. MED. CENT., 550 FIRST AVE., NEW YORK, N.Y. 10016.
SOURCE: LIFE SCI, (1981) 29 (2), 151-156.
CODEN: LIFSAK. ISSN: 0024-3205.
FILE SEGMENT: BA; OLD
LANGUAGE: English

AB The fibrinolytic activity of 2 tumorigenic B16 mouse melanoma lines was stimulated by exogenous hog mucosal or beef lung **heparin** . The activity of 2 normal fibroblast lines was unaffected. The degradation of 125I-fibrin was increased up to 3.6-fold by the addition of **heparin**. Chondroitin-4-sulfate or dextran sulfate did not change the fibrinolytic activity of 3 of the cell lines, but at concentrations where enhancement by **heparin** was much reduced, the activity of one of the B16 melanoma lines was elevated. Antithrombin III did not alter the **plasminogen** activator activity of the B16 cell lines, but in the presence of exogenous **heparin**, the enhancement of fibrinolysis was greatly reduced. The polymers were not cytotoxic during the assay period and had little affect on the plating efficiencies of the lines. The controlled expression of serine proteases is important in many biological processes. One example is the degradation of fibrin by **plasmin** which is generated from **plasminogen**

by **plasminogen** activators. This cellular activity forms a part of the fibrinolytic coagulation scheme. Activation of the coagulation scheme is also associated with **neoplasia**. **Heparin** can form a complex with antithrombin III which greatly accelerates the inactivation of a number of serine proteases, including thrombin, **plasmin** and factors in the fibrinolytic coagulation scheme.

L10 ANSWER 53 OF 56 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 80149438 EMBASE
DOCUMENT NUMBER: 1980149438
TITLE: [Thrombolytic therapy in Paget-v. Schroetter syndrome].
DIE THROMBOLYTISCHE THERAPIE BEIM PAGET-V. SCHROETTER-SYNDROM.
AUTHOR: Trobisch H.; Guenther D.; Bruester Th. H.
CORPORATE SOURCE: Inst. Blutgerinnungswesen Transf. Med., Univ. 4000 Dusseldorf, Germany
SOURCE: Aktuelle Chirurgie, (1980) 15/3 (139-152).
CODEN: AKCHB2
COUNTRY: Germany
DOCUMENT TYPE: Journal
FILE SEGMENT: 037 Drug Literature Index
025 Hematology
014 Radiology
009 Surgery
LANGUAGE: German
SUMMARY LANGUAGE: English

AB Streptokinase activates the conversion of **plasminogen** into **plasmin** in the thrombus; this is a two-phase reaction via a mediator formed by streptokinase and **plasminogen**. Urokinase activates the conversion of **plasminogen** into **plasmin** in a single phase reaction. **Plasmin** destroys fibrin fibrilla by removing elemental units. Fibrin split products X, Y, D, and E were identified. The Paget-v.Schroetter syndrome involves spontaneous thrombosis of the v. subclavica and v. axillaris. There is a symptomatic thrombosis through **tumours**, substernal strumae and aneurysms; it can be iatrogenic as a result of central venous catheterisation and transvenous pacemaker electrodes. Within a few hours there is an increasing swelling of the arm with venous stasis. Pathognomonic proof can be collected by means of phlebography. Thrombolysis is urgently indicated. The following contraindications are mentioned: hypertonia; diabetes; recent traumas; surgery in the spinal canal region; pretreatment with anticoagulants; and, a previous history of streptococcal infection. A preliminary examination with regard to coagulation physiology is necessary. The initial dose is 250000 units streptokinase, later 10000 units per hour which can be reduced by 25% - 50% if the **plasminogen** level drops. After 6 to 7 days a changeover to **heparin** anticoagulation is advised. With regard to urokinase thrombolysis, initially a dose of 250000-500000 is recommended and a maintenance dose of 75000-15000 units per hour. Successful lysis is indicated by a regression of clinical signs. The results generally depend on the age of the thrombus; there is a 100% restitution in three days with a refractory period of up to the 12th day; a late lysis is possible.

L10 ANSWER 54 OF 56 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.

DUPLICATE 18
ACCESSION NUMBER: 1977:205431 BIOSIS
DOCUMENT NUMBER: BA64:27795
TITLE: THE EXTRACT FROM THE TISSUE OF GASTRIC **CANCER** AS PRO COAGULANT IN DISSEMINATED INTRA VASCULAR COAGULATION SYNDROME.
AUTHOR(S): SAKURAGAWA N; TAKAHASHI K; HOSHIYAMA M; JIMBO C; ASHIZAWA K; MATSUOKA M; OHNISHI Y
SOURCE: THROMB RES, (1977) 10 (3), 457-463.
CODEN: THBRAA. ISSN: 0049-3848.
FILE SEGMENT: BA; OLD
LANGUAGE: Unavailable
AB Tissue extracts from 2 histopathologic types of surgically removed human gastric **cancer** were investigated for procoagulant and fibrinolytic activities. Procoagulant activity was due to a thromboplastin-like substance; 1 mg of the extract protein was equivalent to 0.014 mg of Lyoplastin (thromboplastin). It is inhibited by **heparin**, Trasylol and is partially inactivated by heating at 100.degree. C for 10 min, but not at 56 and 37.degree. C. The extracts had **plasminogen** activator and **plasmin** activities. The fibrinolytic activity was inhibited by soybean trypsin inhibitor, Trasylol, and t-AMCHA [trans-aminomethylcyclohexanecarboxylic acid]. In 12 cases studied, 9 were of adenocarcinoma and 3 were **carcinoma** simplex. Procoagulant and fibrinolytic activities appeared to be greatest in the extracts from adenocarcinoma, as compared to those from **carcinoma** simplex or normal tissue surrounding the lesions.

L10 ANSWER 55 OF 56 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 75010144 EMBASE
DOCUMENT NUMBER: 1975010144
TITLE: Experimental studies on the spread of **cancer**, with special reference to fibrinolytic agents and anticoagulants.
AUTHOR: Wood Jr S.
CORPORATE SOURCE: Dept. Exp. Pathol., Merck Inst. Therapeut. Res., Rahway, N.J., United States
SOURCE: Journal of Medicine, (1974) 5/1-3 (7-22).
CODEN: JNMDBO
DOCUMENT TYPE: Journal
FILE SEGMENT: 037 Drug Literature Index
016 Cancer
025 Hematology
LANGUAGE: English
AB The author summarized experiments using anticoagulants or fibrinolytic agents to diminish metastasis formation. The specific anticoagulants studied include **heparin**, dicoumarol, warfarin, arvin and an inhibitor of factor XIII. The fibrinolytic agents used include **plasmin** (streptokinase activated **plasminogen** and urokinase activated **plasminogen**) as well as various preparations of urokinase. In general these data support the concept stated in 1958 that 'the formation of metastases from bloodborne **cancer** cells appears to be intimately related to, or perhaps dependent upon, the coagulation system'. At present, two important considerations have emerged to explain more completely the antimetastatic effects of these agents with safe therapeutic indices: the facilitation of the microcirculation within **tumors**, and the direct as well as the indirect specific and

selective actions that these agents may exert on **cancer** cells as well as the host. These agents have been and are now being evaluated in patients with various types and stages of **cancer**. From the available clinical data, warfarin is used alone before, during and after surgical removal of **tumors**, or alone in patients with early **cancer**, or in patients in remission after intensive cytotoxic chemotherapeutic compounds or radiation therapy. These agents, particularly warfarin or **heparin**, appear to enhance the efficacy of chemotherapy with cytotoxic agents or radiotherapy in patients with various types of **cancer**, including stage III and IV disease. The important mechanisms by which this apparent drug synergism occurs remain to be evaluated. The precise role of broad spectrum agents that alter the aggregation of platelets and that may influence **tumor** growth or metastasis formation in animals and in patients remains an uncertain but important consideration.

L10 ANSWER 56 OF 56 MEDLINE
ACCESSION NUMBER: 70209906 MEDLINE
DOCUMENT NUMBER: 70209906 PubMed ID: 4246344
TITLE: The effect of agents altering haemostasis on the evolution of **tumours** in mice.
AUTHOR: Bresson M L; Cattan A; Hayat M
SOURCE: REVUE EUROPEENNE D ETUDES CLINIQUES ET BIOLOGIQUES, (1970 Apr) 15 (4) 442-3.
Journal code: 0351323. ISSN: 0035-3019.
PUB. COUNTRY: France
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 197008
ENTRY DATE: Entered STN: 19900101
Last Updated on STN: 19900101
Entered Medline: 19700806

FILE 'HCAPLUS' ENTERED AT 15:18:41 ON 26 JUN 2003
L1 3 SEA FILE=REGISTRY ABB=ON PLU=ON "LYS-PLASMINOGEN"?/CN
L2 674 SEA FILE=REGISTRY ABB=ON PLU=ON PLASMINOGEN ?/CN
L3 1 SEA FILE=REGISTRY ABB=ON PLU=ON HEPARIN/CN
L4 1307 SEA FILE=HCAPLUS ABB=ON PLU=ON (L1 OR L2 OR PLASMINOGEN) AND (L3 OR HEPARIN)
L5 41 SEA FILE=REGISTRY ABB=ON PLU=ON PLASMIN ?/CN
L6 1 SEA FILE=REGISTRY ABB=ON PLU=ON "TRANEXAMIC ACID"/CN
L7 301 SEA FILE=HCAPLUS ABB=ON PLU=ON L4 AND (L5 OR L6 OR PLASMIN OR TRANEXAMIC)
L11 6 SEA FILE=HCAPLUS ABB=ON PLU=ON L7 AND (K1 OR K3 OR (KRINGLE OR K)(W)(1 OR 3))

L12 6 L11 NOT L8

L12 ANSWER 1 OF 6 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2001:216376 HCAPLUS
DOCUMENT NUMBER: 134:308548
TITLE: A truncated **plasminogen** activator inhibitor-1 protein induces and inhibits angiostatin (**kringles 1**-3), a **plasminogen** cleavage product

AUTHOR(S): Mulligan-Kehoe, Mary Jo; Wagner, Robert; Wieland, Courtney; Powell, Richard
CORPORATE SOURCE: Division of Vascular Surgery, Department of Surgery, Dartmouth Medical School, Dartmouth College, Hanover, NH, 03756, USA
SOURCE: Journal of Biological Chemistry (2001), 276(11), 8588-8596
CODEN: JBCHA3; ISSN: 0021-9258
PUBLISHER: American Society for Biochemistry and Molecular Biology
DOCUMENT TYPE: Journal
LANGUAGE: English

AB **Plasminogen** activator inhibitor-1 (PAI-1) is a serpin protease inhibitor that binds **plasminogen** activators (uPA and tPA) at a reactive center loop located at the carboxyl-terminal amino acid residues 320-351. The loop is stretched across the top of the active PAI-1 protein maintaining the mol. in a rigid conformation. In the latent PAI-1 conformation, the reactive center loop is inserted into one of the beta sheets, thus making the reactive center loop unavailable for interaction with the **plasminogen** activators. We truncated porcine PAI-1 at the amino and carboxyl termini to eliminate the reactive center loop, part of a **heparin** binding site, and a vitronectin binding site. The region we maintained corresponds to amino acids 80-265 of mature human PAI-1 contg. binding sites for vitronectin, **heparin** (partial), uPA, tPA, fibrin, thrombin, and the helix F region. The interaction of "inactive" PAI-1, rPAI-123, with **plasminogen** and uPA induces the formation of a proteolytic protein with angiostatin properties. Increasing amts. of rPAI-123 inhibit the proteolytic angiostatin fragment. Endothelial cells exposed to exogenous rPAI-123 exhibit reduced proliferation, reduced tube formation, and 47% apoptotic cells within 48 h. Transfected endothelial cells secreting rPAI-123 have a 30% redn. in proliferation, vastly reduced tube formation, and a 50% redn. in cell migration in the presence of VEGF. These two studies show that rPAI-123 interactions with uPA and **plasminogen** can inhibit **plasmin** by two mechanisms. In one mechanism, rPAI-123 cleaves **plasmin** to form a proteolytic angiostatin-like protein. In a second mechanism, rPAI-123 can bind uPA and/or **plasminogen** to reduce the no. of uPA and **plasminogen** interactions, hence reducing the amt. of **plasmin** that is produced.

IT **140208-23-7P, Plasminogen** activator inhibitor 1
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); PRP (Properties); PUR (Purification or recovery); BIOL (Biological study); PREP (Preparation)
(truncated **plasminogen** activator inhibitor-1 protein induces and inhibits **plasminogen** cleavage product angiostatin by binding to **plasminogen** and uPA)

IT **9001-91-6, Plasminogen**
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(truncated **plasminogen** activator inhibitor-1 protein induces and inhibits **plasminogen** cleavage product angiostatin by binding to **plasminogen** and uPA)

REFERENCE COUNT: 71 THERE ARE 71 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE

IN THE RE FORMAT

L12 ANSWER 2 OF 6 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2000:879829 HCAPLUS
DOCUMENT NUMBER: 135:157472
TITLE: A prodrug approach for delivery of t-PA: Construction of the cationic t-PA prodrug by a recombinant method and preliminary in vitro evaluation of the construct
AUTHOR(S): Song, Hui; Liang, Jun F.; Yang, Victor C.
CORPORATE SOURCE: College of Pharmacy, The University of Michigan, Ann Arbor, MI, 48109-1065, USA
SOURCE: ASAIO Journal (2000), 46(6), 663-668
CODEN: AJOUET; ISSN: 1058-2916
PUBLISHER: Lippincott Williams & Wilkins
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Previously, we reported a novel prodrug approach, that could lead to targeted thrombolysis without the risk of bleeding. The approach consists of a protein conjugate made of two components: a fibrin targeting antibody (Ab) linked to an anionic **heparin**, and a **plasminogen** activator (PA) derivatized with cationic species. These two components are linked by means of an electrostatic interaction. Because the cationic species are small, the modified PA would retain its thrombolytic activity. However, this activity would be inhibited after binding to the counterpart due to the blockage of the PA active site by the appended macromols. Because protamine is a clin. antagonist to **heparin**, it can be used in humans to dissoc. the modified PA from its counterpart. Thus, the approach would permit the administration of a fibrin targeting but inactive thrombolytic drug (thereby alleviating the bleeding risk by avoiding systemic generation of **plasmin**), and subsequently a triggered release of the active drug to the fibrin deposit. In our previous work, we demonstrated the feasibility of the approach by producing a pos. charged PA by means of chem. conjugation of a cationic CRRRRRRR peptide with urokinase. In this study, we further extended our work and produced a similar cationic t-PA by means of a recombinant DNA approach; i.e., by fusion of a poly(Arg)7 peptide to the **kringle-1** domain of t-PA. Results obtained from the restriction enzyme anal. and the Western blot yielded full identification of this recombinant protein. This recombinant poly(Arg)7-modified-t-PA protein conjugate (termed "rmt-PA" hereafter) completely retained the fibrinolytic activity of the original recombinant, unmodified t-PA (termed "rt-PA" hereafter), as measured by the chromogenic assay and fibrin agar lysis assay. The prodrug and triggered release features of the proposed approach were confirmed by partial inhibition of the **plasminogen** activating activity of this protein by **heparin**, and the partial reversal of such inhibition by protamine.
IT **139639-23-9P**, Tissue **plasminogen** activator
RL: BPN (Biosynthetic preparation); BPR (Biological process); BSU (Biological study, unclassified); PEP (Physical, engineering or chemical process); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); PROC (Process); USES (Uses)
(construction of a cationic t-PA prodrug by a recombinant method and in vitro evaluation of the construct)
REFERENCE COUNT: 18 THERE ARE 18 CITED REFERENCES AVAILABLE

FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L12 ANSWER 3 OF 6 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2000:17584 HCAPLUS
DOCUMENT NUMBER: 132:189293
TITLE: Nonpeptide factor Xa inhibitors: I. Studies with SF303 and SK549, a new class of potent antithrombotics
AUTHOR(S): Wong, Pancras C.; Quan, Mimi L.; Crain, Earl J.; Watson, Carol A.; Wexler, Ruth R.; Knabb, Robert M.
CORPORATE SOURCE: Cardiovascular Diseases Research, DuPont Pharmaceuticals Company, Wilmington, DE, USA
SOURCE: Journal of Pharmacology and Experimental Therapeutics (2000), 292(1), 351-357
CODEN: JPETAB; ISSN: 0022-3565
PUBLISHER: American Society for Pharmacology and Experimental Therapeutics
DOCUMENT TYPE: Journal
LANGUAGE: English
AB A series of benzamidine isoxazoline derivs. was evaluated for their inhibitory potency against purified human factor Xa (fXa) and in a rabbit model of arteriovenous shunt thrombosis for their antithrombotic activities, expressed as **K1** and IC50, resp. A highly significant correlation was found between **K1** and IC50 ($r = 0.93$, $P < .0001$). The antithrombotic effects of SF303 [mol. wt. 536; **K1**: fXa, 6.3 nM; thrombin, 3,100 nM; trypsin, 110 nM; tissue **plasminogen** activator >20,000 nM; **plasmin**, 2,500 nM] and SK549 [mol. wt. 546; **K1**: fXa, 0.52 nM; thrombin, 400 nM; trypsin, 45 nM; tissue **plasminogen** activator >33,000 nM; **plasmin**, 890 nM] were compared with recombinant tick anticoagulant peptide [**K1**(fXa) = 0.5 nM], DX-9065a [**K1**(fXa) = 30 nM], and **heparin** or low mol. wt. **heparin** (dalteparin) in a rabbit model of arteriovenous shunt thrombosis. ID50 values for preventing arteriovenous shunt-induced thrombosis were 0.6 .mu.mol/kg/h for SF303, 0.035 .mu.mol/kg/h for SK549, 0.01 .mu.mol/kg/h for recombinant tick anticoagulant peptide, 0.4 .mu.mol/kg/h for DX-9065a, 21 U/kg/h for **heparin**, and 23 U/kg/h for low mol. wt. **heparin**. SK549 produced a concn.-dependent antithrombotic effect with an IC50 of 0.062 .mu.M. To evaluate its potential oral efficacy, SK549 was given intraduodenally at a dose of 5 mg/kg; it produced a peak antithrombotic effect of 59 .+-. 4% with a duration of action greater than 6.7 h. Therefore, our study suggests that SF303, SK549, and their analogs represent a new class of synthetic fXa inhibitors that may be clin. useful as antithrombotic agents.
REFERENCE COUNT: 19 THERE ARE 19 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L12 ANSWER 4 OF 6 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1998:544750 HCAPLUS
DOCUMENT NUMBER: 129:240034
TITLE: **Plasminogen** binds the **heparin** -binding domain of insulin-like growth factor-binding protein-3

AUTHOR(S): Campbell, Phil G.; Durham, Susan K.; Suwanichkul, Adisak; Hayes, James D.; Powell, David R.
CORPORATE SOURCE: Orthopaedic Research Laboratory, Allegheny University of Health Sciences, Pittsburgh, PA, 15212, USA
SOURCE: American Journal of Physiology (1998), 275(2, Pt. 1), E321-E331
CODEN: AJPHAP; ISSN: 0002-9513
PUBLISHER: American Physiological Society
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Limited proteolysis lowers affinity of insulin-like growth factor (IGF)-binding protein (IGFBP)-3 for bound IGFs, resulting in greater IGF bioavailability. **Plasmin** is one of many proteases that cleave IGFBP-3, and the **plasmin** system may regulate IGFBP-3 proteolysis and IGF bioavailability in cultured cells in vitro. A role for the **plasmin** system in IGFBP-3 proteolysis in vivo is suggested by data presented here showing that IGFBP-3 binds **plasminogen** (Pg; Glu-Pg) with a dissocn. const. (Kd) ranging from 1.43 to 3.12 nM. IGF-I and Glu-Pg do not compete for IGFBP-3 binding; instead, the binary IGFBP-3/Glu-Pg complex binds IGF-I with high affinity (Kd = 0.47 nM) to form a ternary complex. Competitive binding studies suggest that the **kringle 1**, 4, and 5 domains of Glu-Pg and the **heparin**-binding domain of IGFBP-3 participate in forming the IGFBP-3/Glu-Pg complex, and other studies show that Glu-Pg in this complex is activated at a normal rate by tissue Pg activator. Importantly, IGFBP-3/Glu-Pg complexes were detected in both human citrate plasma and serum, indicating that these complexes exist in vivo. Binding of IGFBP-3 to Glu-Pg in vivo suggests how Glu-Pg activation can specifically lead to IGFBP-3 proteolysis with subsequent release of IGFs to local target tissues.
IT **105913-11-9**, **Plasminogen** activator
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(**plasminogen** binds the **heparin**-binding domain of IGF-BP-3)
IT **9001-91-6**, Glu-**plasminogen**
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(**plasminogen** binds the **heparin**-binding domain of IGF-BP-3)
IT **9005-49-6**, **Heparin**, biological studies
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(**plasminogen** binds the **heparin**-binding domain of IGF-BP-3)
REFERENCE COUNT: 40 THERE ARE 40 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L12 ANSWER 5 OF 6 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1989:170805 HCAPLUS
DOCUMENT NUMBER: 110:170805
TITLE: Influence of **heparin** and various glycosaminoglycans on activation of single chain urokinase-type **plasminogen** activator (scu-PA) by **plasmin**

AUTHOR(S): Watahiki, Y.; Scully, M. F.; Ellis, V.; Kakkar, V. V.
CORPORATE SOURCE: Sch. Med. Dent., King's Coll., London, SE5 8RX, UK
SOURCE: Fibrinolysis (1989), 3(1), 31-5
CODEN: FBRIE7; ISSN: 0268-9499
DOCUMENT TYPE: Journal
LANGUAGE: English

AB An increase in the rate of activation of single-chain urokinase-type **plasminogen** activator (scu-PA) to 2-chain urokinase (tcu-PA) by **plasmin** caused by **heparin** was mol. mass dependent. A **heparin** fraction of 30 kDa increased the catalytic efficiency of activation by 3.7-fold, as opposed to 1.4-fold by **heparin** of av. mol. wt. All of a range of glycosaminoglycans tested caused some increase in the rate of activation, the largest effect being found with chondroitin sulfate K (glucuronic acid 3-sulfate-N-acetylgalactosmine 4-sulfate), which was twice as potent as unfractionated **heparin**. The increase in rate was due to variation in kcat and Km. This effect was concn. dependent such that Km was decreased at low **heparin** concn., but at a high concn. of **heparin** it increased to beyond that in the absence of **heparin**. A progressive increase in kcat was obsd. with **heparin** concn. **Heparin** also caused an increase in catalytic efficiency of K5 **plasmin** (**kringles** 1-4 removed) suggesting that the obsd. effects may be due to interaction with scu-PA rather than **plasmin**. **Heparin** had no influence on kallikrein activation of scu-PA. The influence of glycosaminoglycans on this reaction may be of importance in controlling the physiol. function of scu-PA.

IT **9005-49-6, Heparin,** biological studies
RL: BIOL (Biological study)
(prourokinase of human activation by **plasmin** acceleration by)

L12 ANSWER 6 OF 6 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1986:202971 HCAPLUS
DOCUMENT NUMBER: 104:202971
TITLE: Purification and characterization of a novel, oligomeric, **plasminogen** kringle 4 binding protein from human plasma: tetranectin
AUTHOR(S): Clemmensen, Inge; Petersen, Lars C.; Kluft, Cornelis
CORPORATE SOURCE: Dep. Clin. Microbiol. Clin. Chem., Hvidovre Hosp., Copehhagen, DK-2650, Den.
SOURCE: European Journal of Biochemistry (1986), 156(2), 327-33
CODEN: EJBCAI; ISSN: 0014-2956
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Purifn. of .alpha.2-**plasmin** inhibitor (.alpha.2PI) from human plasma by affinity chromatog. on **plasminogen** -Sepharose resulted in copurifn. of a contaminating protein with mol. wt. (Mr) 17,000 as judged by SDS-PAGE. This contaminating protein could not be removed from the purified .alpha.2-PI prepn. by several types of gel chromatog. The use of the **kringle** 1-3 part of **plasminogen**, **K**(1 + 2 + 3), bound to Sepharose for affinity chromatog., instead of

plasminogen-Sepharose, resulted in .alpha.2PI prepn. without this contaminant. The contaminating protein interacted specifically with the kringle 4 part of **plasminogen** (K4) and not with **K**(1 + 2 + 3) or miniplasminogen. The K4-binding protein was purified by (NH4)2SO4 pptn., affinity chromatog. on K4-Sepharose, ion-exchange chromatog., and gel filtration on AcA 34. The relative mol. mass of the protein (Mr 68,000) was estd. by gel filtration. This suggests a tetrameric protein composed of 4 subunits (Mr 17,000), that are dissocd. by 1% SDS. Dissocn. into subunits was also demonstrated by gel filtration in the presence of 6M guanidine HCl. A specific antibody was raised in rabbits against the purified protein, and this antibody did not react with any known fibrinolytic components. The pI of the K4-binding protein was 5.8. The 1st 3 N-terminal amino acids were Glu-Pro-Pro. The concn. of the protein in plasma was estd. to be 0.20 .mu.M (15 mg/L). The electrophoretic mobility of the K4-binding protein was shown by crossed immunoelectrophoresis to be influenced by the presence of Ca2+, EDTA, and **heparin**. The protein enhanced **plasminogen** activation catalyzed by tissue-type **plasminogen** activator in the presence of poly(D-lysine). The protein appeared to be a novel plasma protein and was tentatively called tetranectin.

IT **9001-91-6**
RL: BIOL (Biological study)
(kringle 4 region of, tetranectin of human blood plasma binding of)

(FILE 'MEDLINE, BIOSIS, EMBASE, WPIDS, CONFSCI, SCISEARCH, JICST-EPLUS, JAPIO, CANCERLIT' ENTERED AT 15:23:23 ON 26 JUN 2003)

L13 17 S L11
L14 16 S L13 NOT L9
L15 9 DUP REM L14 (7 DUPLICATES REMOVED)

L15 ANSWER 1 OF 9 MEDLINE DUPLICATE 1
ACCESSION NUMBER: 2001290742 MEDLINE
DOCUMENT NUMBER: 21269430 PubMed ID: 11113116
TITLE: A truncated **plasminogen** activator inhibitor-1 protein induces and inhibits angiostatin (**kringles 1**-3), a **plasminogen** cleavage product.
AUTHOR: Mulligan-Kehoe M J; Wagner R; Wieland C; Powell R
CORPORATE SOURCE: Division of Vascular Surgery, Department of Surgery, Dartmouth Medical School, Dartmouth College, Hanover, New Hampshire 03756, USA.. mary.j.mulligan-kehoe@dartmouth.edu
CONTRACT NUMBER: R01-HL59590 (NHLBI)
SOURCE: JOURNAL OF BIOLOGICAL CHEMISTRY, (2001 Mar 16) 276 (11) 8588-96.
Journal code: 2985121R. ISSN: 0021-9258.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200106
ENTRY DATE: Entered STN: 20010625
Last Updated on STN: 20030105
Entered Medline: 20010621

AB **Plasminogen** activator inhibitor-1 (PAI-1) is a serpin

protease inhibitor that binds **plasminogen** activators (uPA and tPA) at a reactive center loop located at the carboxyl-terminal amino acid residues 320-351. The loop is stretched across the top of the active PAI-1 protein maintaining the molecule in a rigid conformation. In the latent PAI-1 conformation, the reactive center loop is inserted into one of the beta sheets, thus making the reactive center loop unavailable for interaction with the **plasminogen** activators. We truncated porcine PAI-1 at the amino and carboxyl termini to eliminate the reactive center loop, part of a **heparin** binding site, and a vitronectin binding site. The region we maintained corresponds to amino acids 80-265 of mature human PAI-1 containing binding sites for vitronectin, **heparin** (partial), uPA, tPA, fibrin, thrombin, and the helix F region. The interaction of "inactive" PAI-1, rPAI-1(23), with **plasminogen** and uPA induces the formation of a proteolytic protein with angiostatin properties. Increasing amounts of rPAI-1(23) inhibit the proteolytic angiostatin fragment. Endothelial cells exposed to exogenous rPAI-1(23) exhibit reduced proliferation, reduced tube formation, and 47% apoptotic cells within 48 h. Transfected endothelial cells secreting rPAI-1(23) have a 30% reduction in proliferation, vastly reduced tube formation, and a 50% reduction in cell migration in the presence of VEGF. These two studies show that rPAI-1(23) interactions with uPA and **plasminogen** can inhibit **plasmin** by two mechanisms. In one mechanism, rPAI-1(23) cleaves **plasmin** to form a proteolytic angiostatin-like protein. In a second mechanism, rPAI-1(23) can bind uPA and/or **plasminogen** to reduce the number of uPA and **plasminogen** interactions, hence reducing the amount of **plasmin** that is produced.

L15 ANSWER 2 OF 9 MEDLINE DUPLICATE 2
ACCESSION NUMBER: 2001205906 MEDLINE
DOCUMENT NUMBER: 20560212 PubMed ID: 11110262
TITLE: A prodrug approach for delivery of t-PA: construction of the cationic t-PA prodrug by a recombinant method and preliminary in vitro evaluation of the construct.
AUTHOR: Song H; Liang J F; Yang V C
CORPORATE SOURCE: College of Pharmacy, The University of Michigan, Ann Arbor 48109-1065, USA.
CONTRACT NUMBER: HL38353 (NHLBI)
HL55461 (NHLBI)
SOURCE: ASAIO JOURNAL, (2000 Nov-Dec) 46 (6) 663-8.
Journal code: 9204109. ISSN: 1058-2916.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200104
ENTRY DATE: Entered STN: 20010417
Last Updated on STN: 20010417
Entered Medline: 20010412

AB Previously, we reported a novel prodrug approach, that could lead to targeted thrombolysis without the risk of bleeding. The approach consists of a protein conjugate made of two components: a fibrin targeting antibody (Ab) linked to an anionic **heparin**, and a **plasminogen** activator (PA) derivatized with cationic species. These two components are linked by means of an electrostatic interaction. Because the cationic species are small,

the modified PA would retain its thrombolytic activity. However, this activity would be inhibited after binding to the counterpart due to the blockage of the PA active site by the appended macromolecules. Because protamine is a clinical antagonist to **heparin**, it can be used in humans to dissociate the modified PA from its counterpart. Thus, the approach would permit the administration of a fibrin targeting but inactive thrombolytic drug (thereby alleviating the bleeding risk by avoiding systemic generation of **plasmin**), and subsequently a triggered release of the active drug to the fibrin deposit. In our previous work, we demonstrated the feasibility of the approach by producing a positively charged PA by means of chemical conjugation of a cationic CRRRRRRR peptide with urokinase. In this study, we further extended our work and produced a similar cationic t-PA by means of a recombinant DNA approach; i.e., by fusion of a poly(Arg)7 peptide to the **kringle-1** domain of t-PA. Results obtained from the restriction enzyme analysis and the Western blot yielded full identification of this recombinant protein. This recombinant poly(Arg)7-modified-t-PA protein conjugate (termed "rmt-PA" hereafter) completely retained the fibrinolytic activity of the original recombinant, unmodified t-PA (termed "rt-PA" hereafter), as measured by the chromogenic assay and fibrin agar lysis assay. The prodrug and triggered release features of the proposed approach were confirmed by partial inhibition of the **plasminogen** activating activity of this protein by **heparin**, and the partial reversal of such inhibition by protamine.

L15 ANSWER 3 OF 9 MEDLINE DUPLICATE 3
ACCESSION NUMBER: 2001128841 MEDLINE
DOCUMENT NUMBER: 20566298 PubMed ID: 11113279
TITLE: Inhibition of **plasmin** activity by sulfated polyvinylalcohol-acrylate copolymers.
AUTHOR: Voros G; Kolev K; Csomor K; Machovich R
CORPORATE SOURCE: Department of Medical Biochemistry, Semmelweis University, Budapest, Hungary.
SOURCE: THROMBOSIS RESEARCH, (2000 Nov 15) 100 (4) 353-61. Journal code: 0326377. ISSN: 0049-3848.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200103
ENTRY DATE: Entered STN: 20010404
Last Updated on STN: 20010404
Entered Medline: 20010301

AB The effect of four sulfated polyvinylalcohol-acrylate copolymers and **heparin** on **plasminogen** activation and on **plasmin** activity is studied. The molecules differing in charge (proportion of negatively charged units 40.5%-73.5% of the total) and in size (5600 Da-8800 Da) accelerate **plasminogen** activation by 2- up to 4-fold at a 7-fold molar excess of the polyvinylacrylates over **plasminogen**. They, however, exert a concentration and charge-dependent effect on **plasmin**: both the amidolytic (half-maximal effect at a 1.33-3.66 molar excess of the polyvinylacrylates) and fibrinolytic (half-maximal effect at 1.23-1.72 molar excess of the polyvinylacrylates) activities of **plasmin** are inhibited. In contrast, **heparin** (a similarly carboxylated and sulfated polymer) and polyvinylacrylates

with a low number of sulfate groups (30% sulfated monomers) at concentrations up to 2.2 microM do not affect **plasminogen** activation and **plasmin** activity in a milieu of physiological ionic strength. Experiments with **plasmin** derivatives lacking N-terminal peptides of different length (des-**kringle**(1-4) and des-**kringle**(1-5) **plasmin**) show identical changes in the protease activities, precluding involvement of the kringle-domain in the interaction with the polyvinylacrylates. Fluorescence studies evidence the charge-dependent binding of the polyvinylacrylates to **plasmin**, but not to **plasminogen**. Thus, through non-covalent interaction with the protease-domain of **plasmin** the polyvinylacrylates inhibit fibrinolysis. Since these sulfated copolymers inhibit both thrombin [4] and **plasmin** activity, they may be a useful therapeutic tool in situations when both the blood coagulation and the fibrinolytic system are activated (such as intravascular coagulation and fibrinolysis, ICF).

L15 ANSWER 4 OF 9 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 2000018104 EMBASE
TITLE: Nonpeptide factor Xa inhibitors: I. Studies with SF303 and SK549, a new class of potent antithrombotics.
AUTHOR: Wong P.C.; Quan M.L.; Crain E.J.; Watson C.A.; Wexler R.R.; Knabb R.M.
CORPORATE SOURCE: Dr. P.C. Wong, DuPont Pharmaceuticals Company, P.O. Box 80400, Wilmington, DE 19880-0400, United States. pancras.c.wong@dupontpharma.com
SOURCE: Journal of Pharmacology and Experimental Therapeutics, (2000) 292/1 (351-357).
Refs: 19
ISSN: 0022-3565 CODEN: JPETAB
COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 025 Hematology
030 Pharmacology
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English

AB A series of benzamidine isoxazoline derivatives was evaluated for their inhibitory potency against purified human factor Xa (fXa) and in a rabbit model of arteriovenous shunt thrombosis for their antithrombotic activities, expressed as **K1** and IC50, respectively. A highly significant correlation was found between **K1** and IC50 ($r = 0.93$, $P < .0001$). The antithrombotic effects of SF303 [mol. wt. 536; **K1**; fXa, 6.3 nM; thrombin, 3,100 nM; trypsin, 110 nM; tissue **plasminogen** activator >20,000 nM; **plasmin**, 2,500 nM] and SK549 [mol. wt. 546; **K1**; fXa, 0.52 nM; thrombin, 400 nM; trypsin, 45 nM; tissue **plasminogen** activator >33,000 nM; **plasmin**, 890 nM] were compared with recombinant tick anticoagulant peptide [**K1**(fXa) = 0.5 nM], DX-9065a [**K1**(fXa) = 30 nM], and **heparin** or low molecular weight **heparin** (dalteparin) in a rabbit model of arteriovenous shunt thrombosis. ID50 values for preventing arteriovenous shunt-induced thrombosis were 0.6 .mu.mol/kg/h for SF303, 0.035 .mu.mol/kg/h for SK549, 0.01 .mu.mol/kg/h for recombinant tick anticoagulant peptide, 0.4 .mu.mol/kg/h for DX-9065a, 21 U/kg/h for **heparin**, and 23

U/kg/h for low molecular weight **heparin**. SK549 produced a concentration-dependent antithrombotic effect with an IC50 of 0.062 .mu.M. To evaluate its potential oral efficacy, SK549 was given intraduodenally at a dose of 5 mg/kg; it produced a peak antithrombotic effect of 59 .+-. 4% with a duration of action greater than 6.7 h. Therefore, our study suggests that SF303, SK549, and their analogs represent a new class of synthetic fXa inhibitors that may be clinically useful as antithrombotic agents.

L15 ANSWER 5 OF 9 MEDLINE DUPLICATE 4
ACCESSION NUMBER: 1998365324 MEDLINE
DOCUMENT NUMBER: 98365324 PubMed ID: 9688635
TITLE: **Plasminogen** binds the **heparin**-binding domain of insulin-like growth factor-binding protein-3.
AUTHOR: Campbell P G; Durham S K; Suwanichkul A; Hayes J D; Powell D R
CORPORATE SOURCE: Orthopaedic Research Laboratory, Allegheny University of Health Sciences, Pittsburgh, Pennsylvania 15212, USA.
CONTRACT NUMBER: RO1-DK-38773 (NIDDK)
SOURCE: AMERICAN JOURNAL OF PHYSIOLOGY, (1998 Aug) 275 (2 Pt 1) E321-31.
Journal code: 0370511. ISSN: 0002-9513.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199809
ENTRY DATE: Entered STN: 19980925
Last Updated on STN: 19980925
Entered Medline: 19980916

AB Limited proteolysis lowers affinity of insulin-like growth factor (IGF)-binding protein (IGFBP)-3 for bound IGFs, resulting in greater IGF bioavailability. **Plasmin** is one of many proteases that cleave IGFBP-3, and the **plasmin** system may regulate IGFBP-3 proteolysis and IGF bioavailability in cultured cells in vitro. A role for the **plasmin** system in IGFBP-3 proteolysis in vivo is suggested by data presented here showing that IGFBP-3 binds **plasminogen** (Pg; Glu-Pg) with a dissociation constant (Kd) ranging from 1.43 to 3.12 nM. IGF-I and Glu-Pg do not compete for IGFBP-3 binding; instead, the binary IGFBP-3/Glu-Pg complex binds IGF-I with high affinity (Kd = 0. 47 nM) to form a ternary complex. Competitive binding studies suggest that the **kringle 1**, 4, and 5 domains of Glu-Pg and the **heparin**-binding domain of IGFBP-3 participate in forming the IGFBP-3/Glu-Pg complex, and other studies show that Glu-Pg in this complex is activated at a normal rate by tissue Pg activator. Importantly, IGFBP-3/Glu-Pg complexes were detected in both human citrate plasma and serum, indicating that these complexes exist in vivo. Binding of IGFBP-3 to Glu-Pg in vivo suggests how Glu-Pg activation can specifically lead to IGFBP-3 proteolysis with subsequent release of IGFs to local target tissues.

L15 ANSWER 6 OF 9 SCISEARCH COPYRIGHT 2003 THOMSON ISI
ACCESSION NUMBER: 1998:607297 SCISEARCH
THE GENUINE ARTICLE: 106ZE
TITLE: **Plasminogen** binds the **heparin**

-binding domain of insulin-like growth factor-binding protein-3

AUTHOR: Campbell P G; Durham S K; Suwanichkul A; Hayes J D; Powell D R (Reprint)

CORPORATE SOURCE: TEXAS CHILDRENS HOSP, FEIGIN CTR, MC 3-2482, 6621 FANNIN, HOUSTON, TX 77030 (Reprint); ALLEGHENY UNIV HLTH SCI, ORTHOPAED RES LAB, PITTSBURGH, PA 15212; BAYLOR COLL MED, DEPT PEDIAT, HOUSTON, TX 77030

COUNTRY OF AUTHOR: USA

SOURCE: AMERICAN JOURNAL OF PHYSIOLOGY-ENDOCRINOLOGY AND METABOLISM, (AUG 1998) Vol. 38, No. 2, pp. E321-E331

Publisher: AMER PHYSIOLOGICAL SOC, 9650 ROCKVILLE PIKE, BETHESDA, MD 20814.

ISSN: 0193-1849.

DOCUMENT TYPE: Article; Journal

FILE SEGMENT: LIFE

LANGUAGE: English

REFERENCE COUNT: 40

ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB Limited proteolysis lowers affinity of insulin-like growth factor (IGF)-binding protein (IGFBP)-3 for bound IGFs, resulting in greater IGF bioavailability. **Plasmin** is one of many proteases that cleave IGFBP-3, and the **plasmin** system may regulate IGFBP-3 proteolysis and IGF bioavailability in cultured cells in vitro. A role for the **plasmin** system in IGFBP-3 proteolysis in vivo is suggested by data presented here showing that IGFBP-3 binds **plasminogen** (Pg; Glu-Pg) with a dissociation constant (K-d) ranging from 1.43 to 3.12 nM. IGF-I and Glu-Pg do not compete for IGFBP-3 binding; instead, the binary IGFBP-3/Glu-Pg complex binds IGF-I with high affinity (K-d = 0.47 nM) to form a ternary complex. Competitive binding studies suggest that the **kringle 1**, 4, and 5 domains of Glu-Pg and the **heparin**-binding domain of IGFBP-3 participate in forming the IGFBP-3/Glu-Pg complex, and other studies show that Glu-Pg in this complex is activated at a normal rate by tissue Pg activator. Importantly, IGFBP-3/Glu-Pg complexes were detected in both human citrate plasma and serum, indicating that these complexes exist in vivo. Binding of IGFBP-3 to Glu-Pg in vivo suggests how Glu-Pg activation can specifically lead to IGFBP-3 proteolysis with subsequent release of IGFs to local target tissues.

L15 ANSWER 7 OF 9 MEDLINE DUPLICATE 5

ACCESSION NUMBER: 96195681 MEDLINE

DOCUMENT NUMBER: 96195681 PubMed ID: 8612645

TITLE: Limited **plasmin** proteolysis of vitronectin. Characterization of the adhesion protein as morpho-regulatory and angiostatin-binding factor.

AUTHOR: Kost C; Benner K; Stockmann A; Linder D; Preissner K T

CORPORATE SOURCE: Haemostasis Research Unit, Kerckhoff-Klinik, Bad Nauheim, Germany.

SOURCE: EUROPEAN JOURNAL OF BIOCHEMISTRY, (1996 Mar 1) 236 (2) 682-8.

Journal code: 0107600. ISSN: 0014-2956.

PUB. COUNTRY: GERMANY: Germany, Federal Republic of

DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)

LANGUAGE: English

FILE SEGMENT: Priority Journals
ENTRY MONTH: 199606
ENTRY DATE: Entered STN: 19960613
Last Updated on STN: 19980206
Entered Medline: 19960603

AB The adhesion protein vitronectin is associated with extracellular matrices and serves as cofactor for **plasminogen**-activator inhibitor-1. Limited proteolysis by **plasmin** converts vitronectin into defined fragments which are detectable at sites of inflammation and angiogenesis. The loss and gain of binding functions of vitronectin fragments for macromolecular ligands was characterized in the present study. The initially generated 61--63-kDa vitronectin-(1--348)-fragment serves as typical binding component for **plasminogen** and binding function was lost upon carboxypeptidase B treatment indicating the importance of a C-terminal lysine. Complementary binding sites reside in isolated **plasminogen kringles 1**--3 (designated angiostatin) as deduced from direct binding and ligand blotting experiments. A synthetic vitronectin-(331--348)-peptide from the C-terminus of the 61--63-kDa fragment could mimic **plasminogen** and angiostatin binding. Also, the immobilized peptide bound tissue **plasminogen**-activator and mediated **plasmin** formation, comparable to fibrinogen-derived peptides. The 61--63-kDa vitronectin fragment was indistinguishable in its adhesive properties to intact vitronectin and bound active but not latent **plasminogen**-activator inhibitor-1. Late plasminolysis of vitronectin resulted in the processing of the N-terminal region of the protein with the generation of 42 kDa/35-kDa fragments that had Gly89 as new N-terminus and that were ineffective in promoting cell adhesion. Thus, at sites of cell-matrix interactions which become proteolytically modified by **plasmin** during inflammatory and angiogenic processes, vitronectin serves as **plasminogen**/angiostatin-binding factor. Due to this differential change in functions particularly at sites of deposition in the vascular system or at wound sites vitronectin is considered to be an important morpho-regulatory factor.

L15 ANSWER 8 OF 9 MEDLINE
ACCESSION NUMBER: 90221623 MEDLINE
DOCUMENT NUMBER: 90221623 PubMed ID: 2183168
TITLE: [Thrombotic and hemostatic problems in pregnancy and labor and their significance for the fetus and newborn infant].
Thrombotische und hamostatische Probleme wahrend Schwangerschaft und Geburt und ihre Bedeutung fur Fetus und Neugeborene.
AUTHOR: Astedt B
CORPORATE SOURCE: Frauenklinik, Universitat zu Lund, Schweden.
SOURCE: PADIATRIE UND PADOLOGIE, (1990) 25 (1) 43-53. Ref: 44
Journal code: 0022370. ISSN: 0030-9338.
PUB. COUNTRY: Austria
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LANGUAGE: German
FILE SEGMENT: Priority Journals

ENTRY MONTH: 199005
ENTRY DATE: Entered STN: 19900622
Last Updated on STN: 19900622
Entered Medline: 19900524

AB The following problems are considered: Thrombosis: Safe diagnosis with phlebographic verification is recommended. **Heparin** has been an established treatment with the great advantage that it does not enter the fetal blood stream. In selected cases surgery or thrombolytic therapy has to be considered. Owing to the high risk of recurrence, prophylactic treatment with **Heparin** is required throughout pregnancy. Coumarol derivatives traverse the placental membrane to the foetus and have to be avoided because of a risk for teratogenetic injury and intracranial hemorrhage in the foetus. During the puerperium, warfarin might be given because its concentration in breastmilk is low. However, administration of vitamin **K1** is recommended to prematures. Attention should be given to the side-effects of **Heparin** i.e. thrombocytopenia and osteoporosis. The possibility of antithrombin III deficiency should not be overlooked. In such cases it is also risk of thrombosis in the newborn. Premature separation of placenta: In most cases of abruptio placenta immediate delivery by caesarean section is necessary. In cases with partial separation of placenta and immature foetus, treatment with the fibrinolytic inhibitor **tranexamic** acid (Cyklokapron) has proved useful to prolong pregnancy with maturation of the foetus. Thrombocytopenia: Severe hemorrhage seldom occurs above a level of 50 x 10(9)/l. Treatment with Prednisolon has proved to be of great value. The risk of the child having thrombocytopenia is about 50%. Intraventricular bleedings: Such bleedings mainly occur in prematures. Preliminary results have shown decreased concentrations of specific **plasminogen** activator inhibitors.

L15 ANSWER 9 OF 9 MEDLINE DUPLICATE 6
ACCESSION NUMBER: 86192459 MEDLINE
DOCUMENT NUMBER: 86192459 PubMed ID: 3009181
TITLE: Purification and characterization of a novel, oligomeric, **plasminogen** kringle 4 binding protein from human plasma: tetranectin.
AUTHOR: Clemmensen I; Petersen L C; Kluft C
SOURCE: EUROPEAN JOURNAL OF BIOCHEMISTRY, (1986 Apr 15) 156 (2) 327-33.
Journal code: 0107600. ISSN: 0014-2956.
PUB. COUNTRY: GERMANY, WEST: Germany, Federal Republic of
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 198606
ENTRY DATE: Entered STN: 19900321
Last Updated on STN: 19900321
Entered Medline: 19860606

AB Purification of alpha 2-**plasmin** inhibitor (alpha 2PI) from human plasma by affinity chromatography on **plasminogen** -Sepharose resulted in copurification of a contaminating protein with Mr 17,000 as judged by sodium dodecyl sulphate/polyacrylamide gel electrophoresis. This contaminating protein could not be removed from the purified alpha 2-PI preparation by several types of gel chromatography applied. The use of the **kringle** **1**-3 part of **plasminogen**, **K**(**1** +

2 + 3), bound to Sepharose for affinity chromatography, instead of **plasminogen**-Sepharose, resulted in an alpha 2PI preparation without this contaminant. The contaminating protein was found to interact specifically with the kringle 4 part of **plasminogen** (K4) and not with **K(1** + 2 + 3) or miniplasminogen. The K4-binding protein was purified by ammonium sulphate precipitation, affinity chromatography on K4-Sepharose, ion-exchange chromatography and gel filtration on AcA 34. The relative molecular mass of the protein (Mr 68 000) was estimated by gel filtration. This suggests a tetrameric protein composed of four subunits (Mr 17,000), that are dissociated by 1% sodium dodecyl sulphate. Dissociation into subunits was also demonstrated by gel filtration in the presence of 6 M guanidine hydrochloride. A specific antibody was raised in rabbits against the purified protein and this antibody was shown not to react with any known fibrinolytic components. The pI of the K4-binding protein was found to be 5.8. The first three N-terminal amino acids were determined to be Glu-Pro-Pro. The concentration of the protein in plasma was estimated to be 0.20 +/- 0.03 microM (15 +/- 2 mg/l). The electrophoretic mobility of the K4-binding protein was shown by crossed immunoelectrophoresis to be influenced by the presence of Ca2+, EDTA and **heparin**. The protein was found to enhance **plasminogen** activation catalyzed by tissue-type **plasminogen** activator (t-PA) in the presence of poly(D-lysine). The protein appeared to be a novel plasma protein tentatively called 'tetranectin'.

(FILE 'HCAPLUS, MEDLINE, BIOSIS, EMBASE, WPIDS, CONFSCI, SCISEARCH, JICST-EPLUS, JAPIO, CANCERLIT' ENTERED AT 15:25:41 ON 26 JUN 2003)

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L16         108 S "MORIKAWA W"?/AU
L17       11297 S "MIYAMOTO S"?/AU
L18          11 S L16 AND L17
L19           2 S (L16 OR L17) AND L7
L20          11 S L18 OR L19
L21           7 DUP REM L20 (4 DUPLICATES REMOVED)
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- Author (s)

L21 ANSWER 1 OF 7 HCAPLUS COPYRIGHT 2003 ACS DUPLICATE 1

ACCESSION NUMBER: 2000:241459 HCAPLUS
DOCUMENT NUMBER: 132:275964
TITLE: Novel human aspartase homologous to cathepsin D precursor and use for producing anti-metastasis plasma protein fragments
INVENTOR(S): **Morikawa, Wataru**; Kaminaka, Kazuyoshi; Takemoto, Sumiyo; Maeda, Hiroaki; Nozaki, Chikateru; **Miyamoto, Seiji**
PATENT ASSIGNEE(S): Juridical Foundation the Chemo-Sero-Therapeutic Research Institute, Japan
SOURCE: PCT Int. Appl., 55 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: Japanese
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000020570	A1	20000413	WO 1999-JP5322	19990929
W: US				

RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE

JP 2000106882	A2	20000418	JP 1998-296095	19981002
EP 1118660	A1	20010725	EP 1999-970118	19990929

R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO

PRIORITY APPLN. INFO.: JP 1998-296095 A 19981002
WO 1999-JP5322 W 19990929

AB A novel aspartase, PACE4 (plasminogen angiostatin converting enzyme of pH 4), is prepd. from cell line PC-3 that was established from human prostate cancer and characterized. PACE4 exhibits a mol. wt. of 45 kDa as detd. by non-reducing SDS-PAGE and LVRIPLHKFT at the N-terminus. PACE4 aspartase is highly homol. to human cathepsin D precursor and can degrade plasma proteins such as plasminogen, fibronectin, vitronectin, and human hepatic growth factor into fragments that have the angiostatin-like activities and thus the anti-metastasis effects. A pharmaceutical compn. contg. PACE4 for the prevention of treatment of solid cancers, diabetic retinopathy, or rheumatism is also claimed.

REFERENCE COUNT: 12 THERE ARE 12 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L21 ANSWER 2 OF 7 HCAPLUS COPYRIGHT 2003 ACS DUPLICATE 2
ACCESSION NUMBER: 1998:239304 HCAPLUS
DOCUMENT NUMBER: 128:294008
TITLE: Fragments of **plasminogen** effective in inhibiting tumor metastasis and growth and process for preparing the same
INVENTOR(S): **Morikawa, Wataru; Miyamoto, Seiji**
PATENT ASSIGNEE(S): Juridical Foundation the Chemo-Sero-Therapeutic Research Institute, Japan; Morikawa, Wataru; Miyamoto, Seiji
SOURCE: PCT Int. Appl., 34 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: Japanese
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9815643	A1	19980416	WO 1997-JP3635	19971009

W: AU, CA, KR, US
RW: AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE

JP 10114796	A2	19980506	JP 1996-287651	19961009
AU 9745714	A1	19980505	AU 1997-45714	19971009
US 2002031518	A1	20020314	US 2001-989388	20011121

PRIORITY APPLN. INFO.: JP 1996-287651 A 19961009
WO 1997-JP3635 W 19971009
US 1999-269720 A1 19990406

AB Fragments of a **plasminogen** effective in inhibiting tumor metastasis and growth, an enzymic process for prepg. the fragments, and a tumor metastasis and growth inhibitor contg. the fragments as the active ingredient are presented. The fragments are obtained from the elastase-induced hydrolysis product of Lys-

plasminogen that is obtained by treating a **plasminogen** with **plasmin** and that preferably has a potent **heparin**-binding activity. Alternatively, the Lys-**plasminogen** is prepd. by autolysis of **plasminogen** in the presence of **tranexamic** acid. The inhibitor is useful for clin. therapy of solid cancers typified by lung and colon cancers.

REFERENCE COUNT: 5 THERE ARE 5 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L21 ANSWER 3 OF 7 JAPIO COPYRIGHT 2003 JPO
ACCESSION NUMBER: 1998-114796 JAPIO
TITLE: PLASMID FRAGMENT HAVING INHIBITORY EFFECT ON TUMOR METASTASIS PROLIFERATION AND PREPARATION OF THE SAME
INVENTOR: **MORIKAWA WATARU; MIYAMOTO SEIJI**
PATENT ASSIGNEE(S): CHEMO SERO THERAPEUT RES INST
PATENT INFORMATION:

PATENT NO	KIND	DATE	ERA	MAIN IPC
JP 10114796	A	19980506	Heisei	C07K014-745

APPLICATION INFORMATION
STN FORMAT: JP 1996-287651 19961009
ORIGINAL: JP08287651 Heisei
PRIORITY APPLN. INFO.: JP 1996-287651 19961009
SOURCE: PATENT ABSTRACTS OF JAPAN (CD-ROM), Unexamined Applications, Vol. 1998

AN 1998-114796 JAPIO
AB PROBLEM TO BE SOLVED: To obtain the subject new protein fragment useful for clinical treat ment for solid cancers such as lung cancer and colon cancer, showing **heparin**- binding properties, comprising an elastase decomposition product of lys-**plasminogen**.
SOLUTION: This new **plasminogen** fragment comprises an elastase decomposition product of lys-**plasminogen** and has inhibitory effects on tumor metastasis proliferation and **heparin** binding properties and is useful for clinical treatment for solid cancers represented by lung cancer and colon cancer. The **plasminogen** is obtained by directly adding **plasmin** to a **plasminogen**-containing solution or indirectly and naturally digesting the **plasminogen** by using **tranexamic** acid, etc., to prepare lys-**plasminogen**, then treating the lys **plasminogen** with elastase, passing the decomposition product-containing solution through a carrier using **heparin** as a ligand and adsorbing and eluting.

L21 ANSWER 4 OF 7 HCAPLUS COPYRIGHT 2003 ACS DUPLICATE 3
ACCESSION NUMBER: 1997:719930 HCAPLUS
DOCUMENT NUMBER: 127:362601
TITLE: Method for manufacturing heat-stable, biologically active protein fragments
INVENTOR(S): **Morikawa, Wataru; Miyamoto,**

Seiji
PATENT ASSIGNEE(S): Chemo-Sero-Therapeutic Research Institute, Japan
SOURCE: Jpn. Kokai Tokkyo Koho, 7 pp.
CODEN: JKXXAF
DOCUMENT TYPE: Patent
LANGUAGE: Japanese
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
JP 09286798	A2	19971104	JP 1996-122330	19960419

PRIORITY APPLN. INFO.: JP 1996-122330 19960419

AB A method for manufg. heat-stable, biol. active protein fragments involves: (A) phys. or chem. treatment of a biol. active protein soln. for removal of heat-labile segments and (B) inactivation of viruses in the resultant products, i.e. plasminogen degrdn. products, plasminogen lysine binding site and fibronectin heparin binding site, by low-temp. sterilization in the presence of sugars, amino acids, .epsilon.-aminocaproic acid or their salts.

L21 ANSWER 5 OF 7 HCAPLUS COPYRIGHT 2003 ACS DUPLICATE 4
ACCESSION NUMBER: 1997:580744 HCAPLUS
DOCUMENT NUMBER: 127:173491
TITLE: Immunoassay of plasminogen degradation product for diagnosis of tumor
INVENTOR(S): **Morikawa, Wataru; Miyamoto, Seiji**
PATENT ASSIGNEE(S): Chemo-sero-therapeutic Research Institute, Japan
SOURCE: Jpn. Kokai Tokkyo Koho, 8 pp.
CODEN: JKXXAF
DOCUMENT TYPE: Patent
LANGUAGE: Japanese
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
JP 09178744	A2	19970711	JP 1996-301364	19961025

PRIORITY APPLN. INFO.: JP 1995-303600 19951027

AB The disclosed immunoassay uses monoclonal antibody specific for lysine-binding sites of plasminogen degrdn. product-a tumor marker. The anal. method also includes elastase digestion and affinity sepn. of plasminogen lysine-binding site I and II from intact plasminogen using affinity chromatog. column contg. anti-plasminogen or affinity gel contg. anti-plasminogen lysine-binding site antibodies. Plasminogen degrdn. products are tumor metastasis inhibitor via angiogenesis inhibition.

L21 ANSWER 6 OF 7 SCISEARCH COPYRIGHT 2003 THOMSON ISI
ACCESSION NUMBER: 89:507217 SCISEARCH
THE GENUINE ARTICLE: AR584
TITLE: THE PREPARATION AND CHARACTERIZATION OF A HIGHLY PURIFIED F-IX CONCENTRATE PREPARED BY UTILIZING A CA++-DEPENDENT ANTI-F-IX MONOCLONAL-ANTIBODY
AUTHOR: AKIMOTO Y (Reprint); **MORIKAWA W**; **MIYAMOTO S**; FUNATSU A; OHASHI K; SUGO T; MATSUDA M

CORPORATE SOURCE: CHEMOSEROTHERAPEUT RES INST, KUMAMOTO, JAPAN; JICHI MED SCH, INST HEMATOL, MINAMI KAWACHI, TOCHIGI 32904, JAPAN
COUNTRY OF AUTHOR: JAPAN
SOURCE: THROMBOSIS AND HAEMOSTASIS, (1989) Vol. 62, No. 1, pp. 215.
DOCUMENT TYPE: Conference; Journal
FILE SEGMENT: LIFE
LANGUAGE: ENGLISH
REFERENCE COUNT: No References

L21 ANSWER 7 OF 7 JAPIO COPYRIGHT 2003 JPO
ACCESSION NUMBER: 2000-106882 JAPIO
TITLE: ENZYME PRODUCING PLASMA PROTEIN HAVING TUMOR METASTASIS AND PROLIFERATION INHIBITORY ACTION AND PLASMA PROTEIN FRAGMENTED BY THE SAME
INVENTOR: **MORIKAWA WATARU**; KAMINAKA KAZUYOSHI; TAKEMOTO SUMIYO; MAEDA HIROAKI; NOZAKI CHIKAHIDE; **MIYAMOTO SEIJI**
PATENT ASSIGNEE(S): CHEMO SERO THERAPEUT RES INST
PATENT INFORMATION:

PATENT NO	KIND	DATE	ERA	MAIN IPC
JP 2000106882	A	20000418	Heisei	C12N015-09

APPLICATION INFORMATION
STN FORMAT: JP 1998-296095 19981002
ORIGINAL: JP10296095 Heisei
PRIORITY APPLN. INFO.: JP 1998-296095 19981002
SOURCE: PATENT ABSTRACTS OF JAPAN (CD-ROM), Unexamined Applications, Vol. 2000

AN 2000-106882 JAPIO
AB PROBLEM TO BE SOLVED: To provide a novel nucleic acid fragment that comprises an enzyme producing fragments of plasma protein that has the inhibitory action of tumor metastasis and proliferation, hydrolyzes plasma protein, for example, plasminogen, fibronectin or the like and is useful for treatment of solid carcinomas. SOLUTION: This is an enzyme producing a novel protein fragment that produces a plasma protein fragment having a molecular weight of about 45 kDa according to a non-reduction system SDS electrophoresis, the amino acid residue at the N- terminus of LVRIPLHKFT, acts on plasma protein in an acidic region of a pH of <=5.0 to produce a fragment of a plasma protein having an inhibitory action of metastasis and proliferation of cancer and is an aspartic acid enzyme having a high homology to cathepsin D precursor or the like. Thus, this enzyme is useful for clinical treatment of solid cancers, for example, lung cancer, colon cancer and the like. This enzyme is obtained by maintaining human prostatic cancer cells (PC-3) in a medium including 10% fetal calf serum, substituting the culture medium with a serum-free medium, when they reach the confluent state, collecting the culture supernatant after culture, followed by centrifugation and filtration.

(FILE 'MEDLINE' ENTERED AT 15:27:38 ON 26 JUN 2003)
L22 5710 SEA FILE=MEDLINE ABB=ON PLU=ON PLASMINOGEN/CT
L23 34784 SEA FILE=MEDLINE ABB=ON PLU=ON HEPARIN/CT

-Key terms

L24 249 SEA FILE=MEDLINE ABB=ON PLU=ON L22 AND L23
L25 5752 SEA FILE=MEDLINE ABB=ON PLU=ON PLASMIN/CT
L26 966 SEA FILE=MEDLINE ABB=ON PLU=ON "TRANEXAMIC ACID"/CT
L27 80 SEA FILE=MEDLINE ABB=ON PLU=ON L24 AND (L25 OR L26)
L28 2 SEA FILE=MEDLINE ABB=ON PLU=ON L27 AND C4./CT

L28 ANSWER 1 OF 2 MEDLINE
AN 1998189141 MEDLINE
TI Sulfated glycosaminoglycans enhance tumor cell invasion in vitro by stimulating plasminogen activation.
AU Brunner G; Reimbold K; Meissauer A; Schirrmacher V; Erkell L J
SO EXPERIMENTAL CELL RESEARCH, (1998 Mar 15) 239 (2) 301-10.
Journal code: 0373226. ISSN: 0014-4827.
AB Metastasizing tumor cells invade host tissues by degrading extracellular matrix constituents. We report here that the highly sulfated glycosaminoglycans, heparin and heparan sulfate, as well as the sulfated polysaccharide, fucoidan, significantly enhanced tumor cell invasion in vitro into fibrin, the basement membrane extract, Matrigel, or through a basement membrane-like extracellular matrix. The enhancement of tumor cell invasion was due to a stimulation of the proteolytic cascade of plasminogen activation since the effect required plasminogen activation and was abolished by inhibitors of urokinase-type plasminogen activator (uPA) or plasmin. Sulfated polysaccharides enhanced five reactions of tumor-cell initiated plasminogen activation in a dose-dependent manner. They amplified plasminogen activation in culture supernatants up to 70-fold by stimulating (i) pro-uPA activation by plasmin and (ii) plasminogen activation by uPA. (iii) In addition, sulfated polysaccharides partially protected plasmin from inactivation by alpha 2-antiplasmin. Sulfated polysaccharides also stimulated tumor-cell associated plasminogen activation, e.g., (iv) cell surface pro-uPA activation by plasmin and (v) plasminogen activation by cell surface uPA. These results suggest that sulfated glycosaminoglycans liberated by tumor-cell mediated extracellular matrix degradation in vivo might amplify pericellular plasminogen activation and locally enhance tumor cell invasion in a positive feedback manner.

L28 ANSWER 2 OF 2 MEDLINE
AN 70209906 MEDLINE
TI The effect of agents altering haemostasis on the evolution of tumours in mice.
AU Bresson M L; Cattan A; Hayat M
SO REVUE EUROPEENNE D ETUDES CLINIQUES ET BIOLOGIQUES, (1970 Apr) 15 (4) 442-3.
Journal code: 0351323. ISSN: 0035-3019.

FILE 'HCAPLUS' ENTERED AT 15:30:02 ON 26 JUN 2003
L29 10 S L7 AND (METASTASIS OR METASTAT?)
L30 1 S L29 NOT (L8 OR L12)

L30 ANSWER 1 OF 1 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1986:531447 HCAPLUS
DOCUMENT NUMBER: 105:131447
TITLE: Involvement of both heparanase and **plasminogen** activator in lymphoma cell-mediated degradation of heparan sulfate in the subendothelial extracellular matrix
AUTHOR(S): Bar-Ner, Matia; Mayer, Michael; Schirrmacher,

Volker; Vlodavsky, Israel
CORPORATE SOURCE: Dep. Radiat., Hadassah Univ. Hosp., Jerusalem, 91 120, Israel
SOURCE: Journal of Cellular Physiology (1986), 128(2), 299-306
CODEN: JCLLAX; ISSN: 0021-9541
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The effect of **plasminogen** on the ability of highly **metastatic** ESb mouse lymphoma cells to degrade heparan sulfate (HS) in the subendothelial extracellular matrix (ECM) was studied. A metabolically sulfate-labeled ECM was incubated with the lymphoma cells, and labeled degrdn. products were analyzed by gel filtration on Sepharose 6B. Heparanase-mediated release of low-mol.-wt. HS cleavage products was stimulated 4-fold in the presence of **plasminogen**. Incubation of **plasminogen** alone with the ECM resulted in its conversion into **plasmin**, which released high-mol.-wt. labeled proteoglycans from the ECM. Heating the ECM abolished its ability to convert **plasminogen** into **plasmin**, yet **plasminogen** stimulated, through its activation by the ESb **plasminogen** activator, heparanase-mediated release of low-mol.-wt. HS fragments. **Heparin** inhibited both the basal and **plasminogen**-stimulated degrdn. of HS side chains, but not the total amt. of labeled material released from the ECM. In contrast, aprotinin inhibited the **plasminogen** -stimulated release of high- as well as low-mol.-wt. material. In the absence of **plasminogen**, degrdn. of heated ECM by ESb cells was completely inhibited by aprotinin, but there was only a partial inhibition of the degrdn. of native ECM and no effect on the degrdn. of sol. HS proteoglycan. Thus, proteolytic activity and heparanase participate synergistically in the sequential degrdn. of ECM HS and the ESb proteolytic activity is crucial for this degrdn. when the ECM-assocd. protease is inactivated. **Plasminogen** may serve as a source for the proteolytic activity that produces a more accessible substrate to the heparanase.

IT **9001-91-6**
RL: BSU (Biological study, unclassified); BIOL (Biological study) (activator, in extracellular matrix heparan sulfate degrdn. by DBA/2 T lymphoma cells)

(FILE 'MEDLINE, BIOSIS, EMBASE, WPIDS, CONFSCI, SCISEARCH, JICST-EPLUS, JAPIO, CANCERLIT' ENTERED AT 15:31:21 ON 26 JUN 2003)

L31 24 S L29
L32 3 S L31 NOT (L9 OR L14)
L33 1 DUP REM L32 (2 DUPLICATES REMOVED)

L33 ANSWER 1 OF 1 MEDLINE DUPLICATE 1
ACCESSION NUMBER: 86278456 MEDLINE
DOCUMENT NUMBER: 86278456 PubMed ID: 2426287
TITLE: Involvement of both heparanase and **plasminogen** activator in lymphoma cell-mediated degradation of heparan sulfate in the subendothelial extracellular matrix.
AUTHOR: Bar-Ner M; Mayer M; Schirrmacher V; Vlodavsky I
CONTRACT NUMBER: RO1-CA30289 (NCI)
SOURCE: JOURNAL OF CELLULAR PHYSIOLOGY, (1986 Aug) 128 (2) 299-306.

Journal code: 0050222. ISSN: 0021-9541.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 198609
ENTRY DATE: Entered STN: 19900321
Last Updated on STN: 19970203
Entered Medline: 19860917

AB The effect of **plasminogen** on the ability of highly **metastatic** ESb mouse lymphoma cells to degrade heparan sulfate (HS) in the subendothelial extracellular matrix (ECM) was studied. A metabolically sulfate-labeled ECM was incubated with the lymphoma cells, and labeled degradation products were analyzed by gel filtration on Sepharose 6B. Heparanase-mediated release of low-Mr (0.5 less than Kav less than 0.85) HS cleavage products was stimulated fourfold in the presence of **plasminogen.** Incubation of **plasminogen** alone with the ECM resulted in its conversion into **plasmin,** which released high-Mr (Kav less than 0.33) labeled proteoglycans from the ECM. Heating the ECM (80 degrees C, 1 hr) abolished its ability to convert **plasminogen** into **plasmin,** yet **plasminogen** stimulated, through its activation by the ESb **plasminogen** activator, heparanase-mediated release of low-Mr HS fragments. **Heparin** inhibited both the basal and **plasminogen** -stimulated degradation of HS side chains but not the total amount of labeled material released from the ECM. In contrast, aprotinin inhibited the **plasminogen**-stimulated release of high- as well as low-Mr material. In the absence of **plasminogen,** degradation of heated ECM by ESb cells was completely inhibited by aprotinin, but there was only a partial inhibition of the degradation of native ECM and no effect on the degradation of soluble HS proteoglycan. These results demonstrate that proteolytic activity and heparanase participate synergistically in the sequential degradation of ECM HS and that the ESb proteolytic activity is crucial for this degradation when the ECM-associated protease is inactivated. **Plasminogen** may serve as a source for the proteolytic activity that produces a more accessible substrate to the heparanase.

FILE 'HOME' ENTERED AT 15:32:18 ON 26 JUN 2003